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(54) Glycopeptide antibiotic derivatives.

(57) The present invention provides glycopeptide antibiotic derivative compounds. These derivative compounds possess antibacterial activity against a wide variety of bacteria, including activity against vancomycin-resistant isolates. Methods of making and using these glycopeptide antibiotic derivative compounds are also provided.

EP 0 667 353 A1

New improved antibiotics are continually in demand, particularly for the treatment of human diseases. Increased potency, expanded spectrum of bacterial inhibition, increased *in vivo* efficacy, and improved pharmaceutical properties are some of the goals for improved antibiotics.

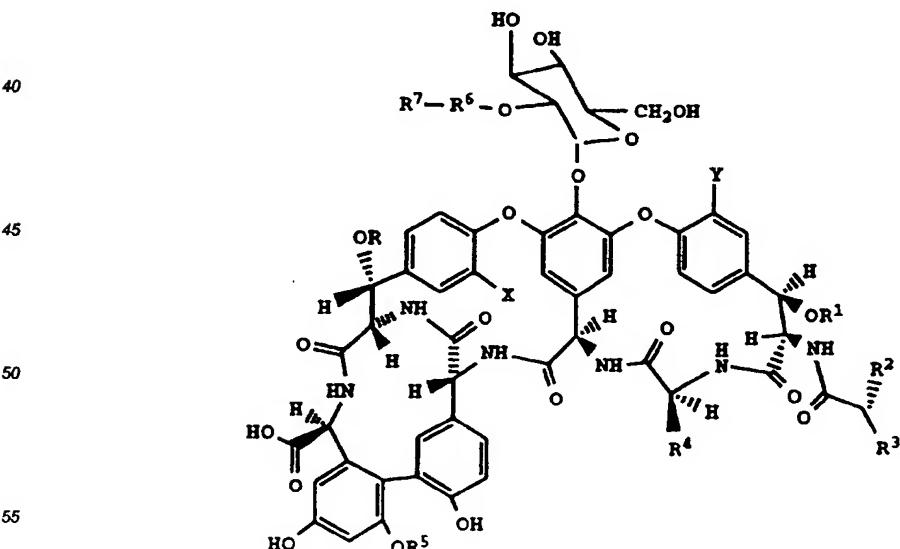
In the search for new antibiotics, structural modification of known antibiotics is attempted when possible. The glycopeptide antibiotics have such complex structures that even small changes are difficult. Furthermore, it is difficult to predict the effect these changes will make in the antimicrobial and physiological properties. Processes for modifying known antibiotics and the new active derivatives made by such processes, therefore, continue to be of great importance.

Previously, N-alkyl and N-acyl derivatives of the glycopeptides vancomycin, A51568A, A51568B, M43A and M43D have been prepared (U.S. Patent Nos. 4,639,433, 4,643,987, and 4,698,327). Several of these compounds exhibited microbiological activity, including activity against vancomycin-resistant isolates. Nicas et al., *Antimicrobial Agents and Chemotherapy*, 33(9):1477-1481 (1989). In addition, European Patent Application Publication No. 0435503, published July 3, 1993, describes certain N-alkyl and N-acyl derivatives of the A82846 glycopeptides, factors A, B, and C.

The formula I compounds of this invention are new members of the glycopeptide group of antibiotics. These new compounds are derivatives of known glycopeptide antibiotics that include vancomycin (U.S. Patent 3,067,099); A82846A, A82846B, and A82846C (U.S. Patent 5,312,738, European Patent Publication 256,071 A1); PA-42867 factors A, C, and D (U.S. Patent 4,946,941 and European Patent Publication 231,111 A2); A83850 (U.S. Patent No. 5,187,082); avoparcin (U.S. Patent 3,38,786 and U.S. Patent 4,322,343); actinoidin, also known as K288 (*J. Antibiotics* Series A 14:141 (1961); helevecardin (*Chem. Abstracts* 110:17188 (1989) and Japanese Patent Application 86/157,397); galacardin (*Chem. Abstracts* 110:17188 (1989) and Japanese Patent Application 89/221,320); and M47767 (European Patent Publication 339,982). The references listed above which describe these glycopeptides are incorporated herein by reference.

Enterococci are important human pathogens. Infections caused by enterococci are generally difficult to treat. Glycopeptides, such as vancomycin and teicoplanin, have become important therapies in the treatment of infections due to enterococci. However, strains of *Enterococcus faecium* and *E. faecalis* have recently been isolated that are resistant to vancomycin and teicoplanin. Leclercq et al., "Plasmid Mediated Resistance to Vancomycin and Teicoplanin in *Enterococcus Faecium*," *The New England Journal of Medicine*, 319(3):157-161 (1988), and Uttley et al., "Vancomycin-Resistant Enterococci," *Lancet*, 1:57-58 (1988). The isolates were also found to be resistant to other antibiotics. A recent survey found 7.9% of Enterococci in United States hospitals are now vancomycin resistant. "Nosocomial Enterococci Resistant to Vancomycin" *Morbidity and Mortality Weekly Report* 42 (30):597-598 (1993). In addition to their broad activity against gram-positive organisms, many of the glycopeptide compounds of this invention also exhibit improved antimicrobial activity against vancomycin-resistant isolates.

The present invention provides compounds of the formula I:



or salt thereof, wherein:

X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminyl, actinosaminy, or ristosaminy;

R<sup>1</sup> is hydrogen, or mannose;

R<sup>2</sup> is -NH<sub>2</sub>, -NHCH<sub>3</sub>, or -N(CH<sub>3</sub>)<sub>2</sub>;

5 R<sup>3</sup> is -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, [*p*-OH, *m*-Cl]phenyl, *p*-rhamnose-phenyl, or [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, [*p*-CH<sub>3</sub>O-rhamnose]phenyl;

R<sup>4</sup> is -CH<sub>2</sub>(CO)NH<sub>2</sub>, benzyl, [*p*-OH]phenyl, or [*p*-OH, *m*-Cl]phenyl;

R<sup>5</sup> is hydrogen, or mannose;

R<sup>6</sup> is 4-*epi*-vancosaminy, L-acosaminy, L-ristosaminy, or L-actinosaminy;

10 R<sup>7</sup> is (C<sub>2</sub>-C<sub>10</sub>)alkenyl, (C<sub>2</sub>-C<sub>12</sub>)alkynyl, (C<sub>1</sub>-C<sub>12</sub>)alkyl-R<sub>8</sub>, (C<sub>1</sub>-C<sub>12</sub>)alkyl-halo, (C<sub>2</sub>-C<sub>8</sub>)alkenyl-R<sub>8</sub>, (C<sub>2</sub>-C<sub>8</sub>)alkynyl-R<sub>8</sub>, (C<sub>1</sub>-C<sub>12</sub>)alkyl-O-R<sub>8</sub>, and is attached to the amino group of R<sup>6</sup>;

R<sup>8</sup> is selected from the group consisting of:

a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) hydroxy,

(ii) halo,

(iii) nitro,

(iv) (C<sub>1</sub>-C<sub>6</sub>)alkyl,

(v) (C<sub>1</sub>-C<sub>6</sub>)alkenyl,

20 (vi) (C<sub>1</sub>-C<sub>6</sub>)alkynyl,

(vii) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(viii) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

(ix) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(x) carbo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(xi) carbobenzoyloxy,

(xii) carbobenzoyloxy substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro,

(xiii) a group of the formula -S(O)<sub>n</sub>-R<sup>9</sup>, wherein n' is 0-2 and R<sup>9</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, or phenyl substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro, and

(xiv) a group of the formula -C(O)N(R<sup>10</sup>)<sub>2</sub> wherein each R<sup>10</sup> substituent is independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, phenyl, or phenyl substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro;

b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) halo,

(ii) (C<sub>1</sub>-C<sub>6</sub>)alkyl,

(iii) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(iv) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

(v) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(vi) phenyl,

(vii) thiophenyl,

35 (viii) phenyl substituted with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or nitro,

(ix) carbo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(x) carbobenzoyloxy,

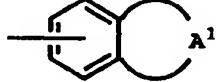
(xi) carbobenzoyloxy substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro,

(xii) a group of the formula -S(O)<sub>n</sub>-R<sup>9</sup>, as defined above,

40 (xiii) a group of the formula -C(O)N(R<sup>10</sup>)<sub>2</sub> as defined above, and

(xiv) thiienyl;

c) a group of the formula:



wherein A<sup>1</sup> is -OC(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-O-, -O-C(A<sup>2</sup>)<sub>2</sub>-O-, -C(A<sup>2</sup>)<sub>2</sub>-O-, or -C(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>, and each A<sup>2</sup> substituent is independently selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, and (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl;

d) a group of the formula:



5

wherein p is from 1 to 5; and

$R^{11}$  is independently selected from the group consisting of:

10

- (i) hydrogen,
- (ii) nitro,
- (iii) hydroxy,
- (iv) halo,
- (v)  $(C_1\text{-}C_8)$ alkyl,
- (vi)  $(C_1\text{-}C_8)$ alkoxy,
- (vii)  $(C_9\text{-}C_{12})$ alkyl,
- (viii)  $(C_2\text{-}C_9)$ alkynyl,
- (ix)  $(C_9\text{-}C_{12})$ alkoxy,
- (x)  $(C_1\text{-}C_3)$ alkoxy substituted with  $(C_1\text{-}C_3)$ alkoxy, hydroxy, halo $(C_1\text{-}C_3)$ alkoxy, or  $(C_1\text{-}C_4)$ alkylthio,
- (xi)  $(C_2\text{-}C_5)$ alkenyloxy,
- (xii)  $(C_1\text{-}C_{13})$ alkenyloxy

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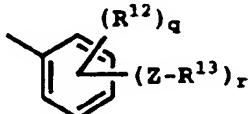
- (xiii) halo- $(C_1\text{-}C_6)$ alkyl,
- (xiv) halo- $(C_1\text{-}C_6)$ alkoxy,
- (xv)  $(C_2\text{-}C_6)$ alkylthio,
- (xvi)  $(C_2\text{-}C_{10})$ alkanoyloxy,
- (xvii) carboxy- $(C_2\text{-}C_4)$ alkenyl,
- (xviii)  $(C_1\text{-}C_3)$ alkylsulfonyloxy,
- (xix) carboxy- $(C_1\text{-}C_3)$ alkyl,
- (xx) N-[di( $C_1\text{-}C_3$ )-alkyl]amino- $(C_1\text{-}C_3)$ alkoxy,
- (xxi) cyano- $(C_1\text{-}C_6)$ alkoxy, and
- (xxii) diphenyl- $(C_1\text{-}C_6)$ alkyl,

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with the proviso that when  $R^{11}$  is  $(C_1\text{-}C_8)$ alkyl,  $(C_1\text{-}C_8)$ alkoxy, or halo, p must be greater or equal to 2, or when  $R^7$  is  $(C_1\text{-}C_3)$ alkyl- $R^8$  then  $R^{11}$  is not hydrogen,  $(C_1\text{-}C_8)$ alkyl,  $(C_1\text{-}C_8)$ alkoxy, or halo;

e) a group of the formula:

35



40

wherein q is 0 to 4;

$R^{12}$  is independently selected from the group consisting of:

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- (i) halo,
- (ii) nitro,
- (iii)  $(C_1\text{-}C_6)$ alkyl,
- (iv)  $(C_1\text{-}C_6)$ alkoxy,
- (v) halo- $(C_1\text{-}C_6)$ alkyl,
- (vi) halo- $(C_1\text{-}C_6)$ alkoxy, and
- (vii) hydroxy, and
- (viii)  $(C_1\text{-}C_6)$ thioalkyl;

50

r is 1 to 5; provided that the sum of q and r is no greater than 5;

Z is selected from the group consisting of:

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- (i) a single bond,
- (ii) divalent  $(C_1\text{-}C_6)$ alkyl unsubstituted or substituted with hydroxy,  $(C_1\text{-}C_6)$ alkyl, or  $(C_1\text{-}C_6)$ alkoxy,
- (iii) divalent  $(C_2\text{-}C_6)$ alkenyl,
- (iv) divalent  $(C_2\text{-}C_6)$ alkynyl, or
- (v) a group of the formula  $-(C(R^{14})_2)_s\text{-}R^{15}\text{-}(C(R^{14})_2)_t-$ , wherein s is 0-6; wherein each  $R^{14}$  substituent is independently selected from hydrogen,  $(C_1\text{-}C_6)$ -alkyl, or  $(C_4\text{-}C_{10})$  cycloalkyl; and  $R^{15}$  is selected from  $\text{-O-}$ ,  $\text{-S-}$ ,  $\text{-SO-}$ ,  $\text{-SO}_2\text{-}$ ,  $\text{-SO}_2\text{O-}$ ,  $\text{-C(O)-}$ ,  $\text{-OC(O)-}$ ,  $\text{-NH-}$ ,  $\text{-N(C}_1\text{-C}_6\text{ alkyl)-}$ , and

-C(O)NH-, -NHC(O)-, N=N;

R<sup>13</sup> is independently selected from the group consisting of:

(i) (C<sub>4</sub>-C<sub>10</sub>)heterocycl,

(ii) h teroaryl,

(iii) (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl unsubstituted or substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, or

(iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, halo-(C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo-(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxyphenyl, phenyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxyphenyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)alkynyl, and (C<sub>1</sub>-C<sub>6</sub>)alkylphenyl;

f) (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) (C<sub>1</sub>-C<sub>6</sub>)alkyl,

(ii) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(iii) (C<sub>1</sub>-C<sub>6</sub>)alkenyl,

(iv) (C<sub>1</sub>-C<sub>6</sub>)alkynyl,

(v) (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl,

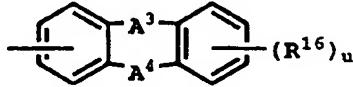
(vi) phenyl,

(vii) phenylthio,

(viii) phenyl substituted by nitro, halo, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy, or carbocycloalkoxy, and

(ix) a group represented by the formula -Z-R<sup>13</sup> wherein Z and R<sup>13</sup> are as defined above; and

g) a group of the formula:



wherein

A<sup>3</sup> and A<sup>4</sup> are each independently selected from

(i) a bond,

(ii) -O-,

(iii) -S(O)<sub>t</sub>, wherein t is 0 to 2,

(iv) -C(R<sup>17</sup>)<sub>2</sub>, wherein each R<sup>17</sup> substituent is independently selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or both R<sup>17</sup> substituents taken together are O,

(v) -N(R<sup>18</sup>)<sub>2</sub>, wherein each R<sup>18</sup> substituent is independently selected from hydrogen; (C<sub>1</sub>-C<sub>6</sub>)alkyl; (C<sub>1</sub>-C<sub>6</sub>)alkenyl; (C<sub>1</sub>-C<sub>6</sub>)alkynyl; (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl; phenyl; phenyl substituted by nitro, halo, (C<sub>1</sub>-C<sub>6</sub>)alkanoyloxy; or both R<sup>18</sup> substituents taken together are (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl;

R<sup>16</sup> is R<sup>12</sup> or R<sup>13</sup> as defined above; and

u is 0-4.

Another aspect of the invention relates to compositions for the treatment of susceptible bacterial infections comprising a compound of formula I in combination with an acceptable pharmaceutical carrier. Methods for the treatment of susceptible bacterial infections with compositions of formula I are also a part of this invention.

The alkyl substituents recited herein denote substituted or unsubstituted, straight or branched chain hydrocarbons of the length specified. The term "alkenyl" refers to a substituted or unsubstituted, straight or branched alkenyl chain of the length specified. The term "alkynyl" refers to a substituted or unsubstituted, straight or branched alkynyl chain of the length specified.

The alkoxy substituents recited herein represent an alkyl group attached through an oxygen bridge. The term "alkenoxy" represents a alkenyl chain of the specified length attached to an oxygen atom.

The term "multicyclic aryl" means a stable, saturated or unsaturated, substituted or unsubstituted, 9 to 10 membered organic fused bicyclic ring; a stable, saturated or unsaturated, substituted or unsubstituted 12 to 14 membered organic fused tricyclic ring; or a stable, saturated or unsaturated, substituted or unsubstituted 14 to 16 membered organic fused tetracyclic ring. The bicyclic ring may have 0 to 4 substituents, the tricyclic ring may have 0 to 6 substituents, and the tetracyclic ring may have 0 to 8 substituents. Typical multi-cyclic aryls include fluorenyl, naphthyl, anthranyl, phenanthranyl, biphenylene and pyrenyl.

The term "heteroaryl" represents a stable, saturated or unsaturated, substituted or unsubstituted, 4 to 7 membered organic monocyclic ring having a hetero atom selected from S, O, and N; a stable, saturated or unsaturated, substituted or unsubstituted, 9 to 10 membered organic fused bicyclic ring having 1 to 2 hetero atoms selected from S, O, and N; or a stable, saturated or unsaturated, substituted or unsubstituted, 12 to 14 membered organic fused tricyclic ring having a hetero atom selected from S, O, and N. The nitrogen and sulfur

atoms of these rings are optionally oxidized, and the nitrogen hetero atoms are optionally quaternized. The monocyclic ring may have 0 to 5 substituents. The bicyclic ring may have 0 to 7 substituents, and the tricyclic ring may have 0 to 9 substituents. Typical heteroaryls include quinolyl, piperidyl, thienyl, piperonyl, oxafluoranyl, pyridyl and benzothienyl and the like.

5 The term "(C<sub>4</sub>-C<sub>10</sub>)cycloalkyl" embraces substituents having from four to ten carbon atoms, such as cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl which may be unsubstituted or substituted with substituents such as alkyl and phenyl. This term also embraces C<sub>6</sub> to C<sub>10</sub> cycloalkenyl groups such as cyclopentenyl and cyclohexenyl. The term "(C<sub>4</sub>-C<sub>10</sub>)cycloalkyl" also embraces bicyclic and tricyclic cycloalkyls such as bicyclopentyl, bicyclohexyl, bicycloheptyl, and adamantly.

10 The term "alkanoyloxy" represents an alkanoyl group attached through an oxygen bridge. These substituents may be substituted or unsubstituted, straight, or branched chains of the specified length.

The term "cyano-(C<sub>1</sub>-C<sub>6</sub>)alkoxy" represents a substituted or unsubstituted, straight or branched alkoxy chain having from one to six carbon atoms with a cyano moiety attached to it.

15 The term "divalent (C<sub>1</sub>-C<sub>6</sub>)alkyl" represents an unsubstituted or substituted, straight or branched divalent alkyl chain having from one to six carbon atoms. Typical divalent (C<sub>1</sub>-C<sub>6</sub>)alkyl groups include methylene, ethylene, propylene, isopropylene, butylene, isobutylene, sec-butylene, t-butylene, pentylene, neo-pentylene, and hexylene. Such divalent (C<sub>1</sub>-C<sub>6</sub>)alkyl groups may be substituted with substituents such as alkyl, alkoxy, and hydroxy.

20 The term "divalent (C<sub>2</sub>-C<sub>6</sub>)alkenyl" represents a straight or branched divalent alkenyl chain having from two to six carbon atoms. Typical divalent (C<sub>2</sub>-C<sub>6</sub>)alkenyl include ethenyl, 1-propenyl, 2-propenyl, 1-but enyl, 2-but enyl and the like.

The term "divalent (C<sub>2</sub>-C<sub>6</sub>)alkynyl" represents a straight or branched divalent alkynyl chain having from two to six carbon atoms. Typical divalent (C<sub>2</sub>-C<sub>6</sub>)alkynyl include ethynylene, 1-propynylene, 2-propynylene, 1-butynylene, 2-butynylene and the like.

25 The term "halo" represents chloro, fluoro, bromo or iodo.

The term "halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl" represents a straight or branched alkyl chain having from one to six carbon atoms with from 0 to 3 halogen atoms attached to each carbon. Typical halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl groups include chloromethyl, 2-bromoethyl, 1-chloroisopropyl, 3-fluoropropyl, 2,3-dibromobutyl, 3-chloroisobutyl, iodo-t-butyl, trifluoromethyl, and the like.

30 The term "halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy" represents a straight or branched alkoxy chain having from one to six carbon atoms with from 0 to 3 halogen atoms attached to each carbon. Typical halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy groups include chloromethoxy, 2-bromoethoxy, 1-chloroisopropoxy, 3-fluoroproxy, 2,3-dibromobutoxy, 3-chloroisobutoxy, iodo-t-butoxy, trifluoromethoxy, and the like.

35 The term "heterocyclyl" embraces saturated groups having three to ten ring members and which heterocyclic ring contains a hetero atom selected from oxygen, sulfur and nitrogen, examples of which are piperazinyl, morpholino, piperidyl, methylpiperidyl, azetidinyl, and aziridinyl.

The invention includes salts of the compounds defined by formula I. Although generally neutral, a compound of this invention can possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a number of inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

40 The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula I which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an inorganic base. Such salts are known as acid addition and base addition salts.

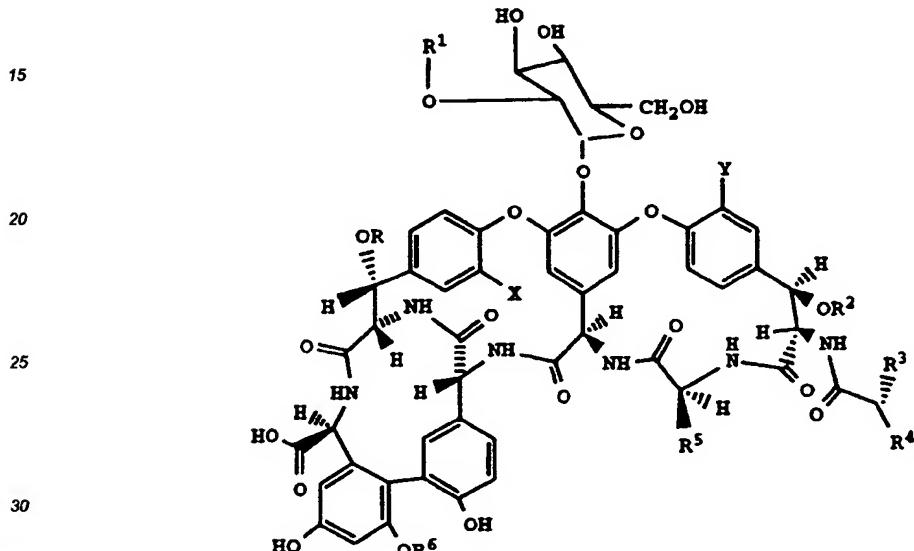
45 Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, acetic acid, and methanesulfonic

acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole.

10 The compounds of the present invention are prepared from compounds of the formula:



35 The compounds of formula II are defined in Table 1.

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**TABLE 1**  
**Formula II Compounds<sup>a</sup>**

	antibiotic	R	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	X	Y
10	vancomycin	H	van	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	C1
A82846A	4-epi	4-epi	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	H	C1	
A82846B	4-epi	4-epi	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	C1	
A82846C	4-epi	4-epi	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	H	H	
PA-42867-A	4-epi	4-epi	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	H	
PA-42867-C	4-epi	4-epi	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	H	H	
PA-42867-D	4-epi	4-epi	H	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	H	
A83850A		H	keto	H	N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	C1
A83850B		H	keto	H	NHCH <sub>3</sub>	CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> (CO)NH <sub>2</sub>	H	C1	C1
actinoidin	actin	acos	H	NH <sub>2</sub>	p-OH,m-Cl-phenyl	benzyl	man	C1	H	
avoparcin	risto	risto	man	N(CH <sub>3</sub> ) <sub>2</sub>	p-rha-phenyl	p-OH-phenyl	H	H	H	
galacardin	risto	risto	man	NHCH <sub>3</sub>	p-gal-gal-phenyl	p-OH-phenyl	H	C1	H	
heleve-cardin	risto	risto	H or man	NHCH <sub>3</sub>	p-CH <sub>3</sub> O-rha-phenyl	p-OH,m-Cl-phenyl	H	C1	H	
M47767	actin	acos	H	NHCH <sub>3</sub>	p-OH,m-Cl-phenyl	benzyl	man	C1	H	

<sup>a</sup>Abbreviations for the formula II compounds are: actin = actinosaminy1; acos =acosaminy1; 4-epi = 4-epi-vancosaminy1; gal = galactosyl; keto = 4-keto-vancosaminy1; man = mannose; rha = rhamnosyl; rha-gal = rhamnosyl-galactosyl; risto = ristosaminy1; van = vancosaminy1.

In a preferred embodiment of the invention, the formula I compounds are prepared from the A82846 antibiotics (A82846A, A82846B, and A82846C) and PA-42867-A. In a more preferred embodiment, the compounds of the present invention are prepared from A82846B ("A82846B derivatives"). A82846B is represented by formula I compounds wherein R is 4-epi-vancosaminy1, R<sup>1</sup> is hydrogen, R<sup>2</sup> is NHCH<sub>3</sub>, R<sup>3</sup> is CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, R<sup>4</sup> is CH<sub>2</sub>(CO)NH<sub>2</sub>, R<sup>5</sup> is hydrogen, R<sup>6</sup> is 4-epi-vancosaminy1 and X and Y are Cl. A82846B derivatives of the present invention having substituents at position R<sup>7</sup> of formula I are listed herein in the manner "R<sup>7</sup>-A82846B". For example, the compound "phenylbenzyl-A82846B" has a phenylbenzyl substituent at position R<sup>7</sup> in formula I.

Preferred formula I compounds include those A82846B derivatives wherein R<sup>7</sup> is -(C<sub>1</sub>-C<sub>12</sub>-alkyl)-R<sup>8</sup>, with -CH<sub>3</sub>-R<sup>8</sup> being more preferred, and R<sup>8</sup> is an unsubstituted multicyclic aryl. Of this group, naphthylmethyl-A82846B, acenaphthlenyl-methyl-A82846B, and fluorenylmethyl-A82846B are more preferred.

Preferred formula I compounds also include those A82846B derivatives wherein R<sup>7</sup> is -(C<sub>1</sub>-C<sub>12</sub>-alkyl)-R<sup>8</sup>, with -CH<sub>3</sub>-R<sup>8</sup> being more preferred, and R<sup>8</sup> is an unsubstituted heteroaryl or a heteroaryl substituted by halo-phenyl. Of this group, [1-oxa]fluorenylmethyl-A82846B, chlorophenylbenzoxazolemethyl-A82846B, and phenylthienylmethyl-A82846B are more preferred.

Further preferred compounds of formula I include those A82846B derivatives wherein R<sup>7</sup> is -(C<sub>1</sub>-C<sub>12</sub>-alkyl)-R<sup>8</sup>, with -CH<sub>3</sub>-R<sup>8</sup> being more preferred, and R<sup>8</sup> is a group of the formula:

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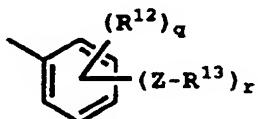


wherein p is 1 and R<sup>11</sup> is selected from (C<sub>2</sub>-C<sub>5</sub>)alkenyloxy, halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, (C<sub>2</sub>-C<sub>10</sub>)alkanoyloxy, (C<sub>1</sub>-C<sub>3</sub>)alkoxy substituted with (C<sub>1</sub>-C<sub>4</sub>)alkylthio, and diphenyl-(C<sub>1</sub>-C<sub>6</sub>)alkyl. Of this group, trifluoromethoxybenzyl-A82846B, diphenylmethylbenzyl-A82846B, thiopropylethoxybenzyl-A82846B, acetoxybenzyl-A82846B, nonanoxyloxybenzyl-A82846B, and tetrafluoroethoxybenzyl-A82846B are more preferred.

Still further preferred compounds of formula I include those A82846B derivatives wherein R<sup>7</sup> is -(C<sub>1</sub>-C<sub>12</sub>-alkyl)-R<sup>8</sup>, with -CH<sub>3</sub>-R<sup>8</sup> being more preferred, and R<sup>8</sup> is a group of the formula:

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wherein q is 1 to 5; r is 1; Z is selected from a single bond, divalent (C<sub>1</sub>-C<sub>6</sub>)alkyl, divalent (C<sub>2</sub>-C<sub>6</sub>)alkenyl, and -R<sup>15</sup>-(C(R<sup>14</sup>)<sub>2</sub>)<sub>s</sub>-, wherein R<sup>15</sup> is selected from -O-, -S-, -SO<sub>2</sub>-, and -OC(O)-, each R<sup>14</sup> substituent is hydrogen, and s is 0 or 1; and R<sup>13</sup> is selected from: (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl; phenyl; and phenyl substituted by nitro, halo, (C<sub>1</sub>-C<sub>10</sub>)alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, or halo(C<sub>1</sub>-C<sub>3</sub>)alkyl. Of this group, chlorophenylbenzyl-A82846B, phenylbenzyl-A82846B, benzylbenzyl-A82846B, methylphenylbenzyl-A82846B, pentylphenylbenzyl-A82846B, methoxyphenylbenzyl-A82846B, pentoxyphenylbenzyl-A82846B, nitrophenoxybenzyl-A82846B, fluorophenoxybenzyl-A82846B, phenylethynylbenzyl-A82846B, phenoxybenzyl-A82846B, benzyloxybenzyl-A82846B, butylphenoxybenzyl-A82846B, chlorophenoxybenzyl-A82846B, chlorobenzyloxybenzyl-A82846B, butylphenoxybenzyl-A82846B, trifluoromethylphenoxybenzyl-A82846B, dichlorophenoxybenzyl-A82846B, nitrobenzyloxybenzyl-A82846B, benzoyloxybenzyl-A82846B, cyclohexyloxybenzyl-A82846B, thiophenylbenzyl-A82846B, chlorophenylsulfonylbenzyl-A82846B, and cyclohexylbenzyl-A82846B, cyclohexylethoxybenzyl-A82846B, chlorophenoxynitrobenzyl-A82846B, benzylmethoxybenzyl-A82846B, chlorophenoxynitrobenzyl-A82846B, and phenoxymethoxybenzyl-A82846B, benzoyloxy-dimethoxybenzyl-A82846B, cyclohexanoyloxydimethylbenzyl-A82846B, trifluoromethylphenylbenzyl-A82846B, butylphenylthiobenzyl-A82846B, and bromophenylbenzyl-A82846B more preferred.

Still further preferred compounds of formula I include A82846B derivatives wherein R<sup>7</sup> is -(C<sub>1</sub>-C<sub>12</sub>-alkyl)-R<sup>8</sup>, with -CH<sub>3</sub>-R<sup>8</sup> being more preferred, and R<sup>8</sup> is (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl substituted with (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl. Of this group of compounds, more preferred is cyclohexyl-cyclohexylmethyl-A82846B and butylcyclohexylmethyl-A82846B.

Formula I compounds that are prepared from A83850A or A83850B can be prepared from the reduced forms of these compounds. The reduced forms of compounds A83850A or A83850B are produced according to the method described in U.S. Pat. No. 5,187,082, which is incorporated herein by reference.

The compounds of this invention are prepared by reacting a formula II compound with an aldehyde to form an intermediate Schiff's base, which is subsequently reduced with a metal borohydride to give the desired N-alkyl amine.

In the first method of making the compounds of this invention, hereinafter Method A (described in Examples 1 and 2), the reaction for the formation of the Schiff's base is carried out under an inert atmosphere, such as nitrogen or argon, in a polar solvent, such as dimethylformamide (DMF) or methanol (MeOH), or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, at a temperature of about 25°C to about 100°C. The reaction is preferably carried out at a temperature from about 60°C to about 70°C for 30 minutes to 2 hours in a mixture of dimethylformamide and methanol, or in methanol. The intermediate Schiff's base is then reduced, preferably without isolation, to produce the corresponding N-alkyl derivative(s). The reduction of the Schiff's base can be effected using a chemical reducing agent such as a metal borohydride, for example, sodium borohydride or sodium cyanoborohydride. The reduction reaction can be carried out in a polar organic solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol. The reduction reaction can be carried out at a temperature of about 25°C to about 100°C for 1 to 5 hours. The reduction reaction is preferably carried out using an excess of sodium cyanobor-

ohydrid in a mixtur of dimethylformamid and methanol or in m thanol at about 60°C to about 70°C for 1 to 2 hours. M thod A is preferable for b nzylic aldehydes.

In a second method of making compounds of this invention, hereinafter Method B (described in Example 3), the formation of the Schiff' bas is carried out under an inert atmospher , such as nitrogen or argon, in the presence of the reducing agent, sodium cyanoborohydride, in a polar solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, at a temperature of about 25°C to about 100°C for 1 to 5 hours. The reaction is preferably carried out at a temperature from about 60°C to about 70°C for 1 to 2 hours in a mixture of dimethylformamide and methanol. Method B is preferable for nonbenzylc aldehydes.

In a third method of making compounds of this invention, hereinafter Method C (described in Example 4), the formation of the Schiff's base is carried out a) under an inert atmosphere, such as nitrogen or argon, b) in the presence of the reducing agent, such as a metal borohydride, with sodium cyanoborohydride being most preferred, or a homogenous or heterogeneous catalytic hydrogenation agent(s), such as Crabtree's catalyst, Wilkinson's catalyst, palladium on carbon, platinum on carbon, or rhodium on carbon, c) in a polar solvent, such as dimethylformamide, methanol, or a mixture of polar solvents, such as a mixture of dimethylformamide and methanol, and d) at a temperature of about 25°C to about 100°C. The reaction is preferably carried out at a temperature from about 60°C to about 70°C in methanol. The reaction is allowed to continue for about 20 to about 28 hours, at which time the reaction mixture is adjusted to about pH 7.5 to about pH 10, with a pH of about 9.0 being preferred. The pH adjustment halts the reaction. Because the product is marginally soluble in polar solvents, the solvent of the reaction can be exchanged to an alcohol such as ethanol, butanol, or isopropanol, with isopropanol being preferred, to allow for precipitation of the product. Method C is a preferred method of this invention in view of the increased product yield provided by this method. Another advantage of this reaction scheme is the increased ratio of preferred product (products substituted at the amino group of the sugar denoted as R<sup>1</sup> in Formula II compounds) to other products (products that are substituted at the amino groups of substituents denoted as R and/or R<sup>3</sup> of the Formula II compounds). By allowing the reaction to proceed for an extended period of time, such as 20 to 28 hours, products that are monosubstituted at positions denoted as R and R<sup>3</sup> in the Formula II compounds are converted to disubstituted forms, making the preferred mono-substituted derivative easier to isolate.

The products of the reaction, obtained from either Method A, B, or C can be purified by preparative reverse-phase HPLC utilizing Waters C18 Nova-Pak columns with ultraviolet light (UV; 235 nm or 280 nm) detection. A 30 minute gradient solvent system consisting of 95% aqueous buffer/5% CH<sub>3</sub>CN at time=0 minutes to 20% aqueous buffer/80% CH<sub>3</sub>CN at time=30 minutes is typically used, where the aqueous buffer is either TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid) or TFA (0.1% trifluoroacetic acid overall concentration).

HPLC analysis of the reaction mixtures and final purified products can be accomplished utilizing a Waters C18 MicroBonda-Pak column (typically 3.9 x 300 mm steel) or Waters Nova-pak C18 RCM column (8 x 100 mm) with UV (235 nm or 280 nm) detection. A 30 minute gradient solvent system consisting of 95% aqueous buffer/5% CH<sub>3</sub>CN at time=0 minute to 20% aqueous buffer/80% CH<sub>3</sub>CN at time=30 minutes is typically used, where the aqueous buffer is either TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid) or TFA (0.1% trifluoroacetic acid overall concentration).

The ratio of the aldehyde to the formula II compound and the reaction conditions determines the products of the reaction. The monosubstituted derivatives are those derivatives where a hydrogen atom of the amino group at position R<sup>1</sup> in formula II is replaced by one of the substituents listed above for formula I. When using Methods A or B, described above, the formation of monosubstituted derivatives substituted at the amino group of the amino sugar at position R<sup>1</sup> in the formula II compounds is favored by using a slight excess of aldehyde, a shorter reaction time, and a lower temperature. As noted above, Method C favors the formation of the mono-substituted derivative. The monosubstituted derivative is preferred. A large excess of the aldehyde favors the formation of disubstituted and trisubstituted derivatives of the formula II compounds. The disubstituted derivatives are the derivatives where a hydrogen atom at two of the locations selected from the amino group at position R<sup>3</sup> and the amino group of the amino sugars designated as R or R<sup>1</sup> in formula II, are replaced by the reduced aldehyde moiety. The trisubstituted derivatives are the derivatives where a hydrogen atom at three of the locations selected from the amino group at position R<sup>3</sup> and the amino group of the amino sugars designated as R or R<sup>1</sup> in formula II, are replaced by the reduced aldehyde moiety.

Examples of compounds that have been prepared and are illustrative of the formula I compounds are listed in Tables 2A and 2B. Table 2A lists compounds prepared by reacting an aldehyde with the glycopeptide A82846B. Table 2A lists the sidechain substitutions on the amino group of the 4-*epi*-vancosaminyl sugar of the 4-*epi*-vancosaminyl-O-glycosyl disaccharide of the A82846B compound. All of the compounds listed are monosubstituted derivativ s.

Table 2B lists those compounds that were prepared by reacting an aldehyde with a variety of glycopaptid antibiotics other than A82846B. The compounds of Table 2B are monosubstituted at the amino group of the amino sugar designated as R<sup>1</sup> in formula II with the sidechain listed. All of the compounds listed are monosubstituted derivatives.

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TABLE 2A

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COMPOUND NO.	SIDECHAIN
1	2-naphthylmethyl
10	4-phenylbenzyl
2	1-naphthylmethyl
15	4-phenoxybenzyl
5	4-benzyloxybenzyl
6	4-trifluoromethoxybenzyl
7	4-allyloxybenzyl
8	4-nonyloxybenzyl
20	2-methoxy-1-naphthylmethyl
9	4-dodecyloxybenzyl
10	9-phenanthranyl methyl
11	4-decyloxybenzyl
25	9-anthranyl methyl
12	4-[phenylethynyl]4-phenylbenzyl
13	4-methoxy-1-naphthylmethyl
30	1-pyrenylmethyl
14	9-[10-methyl]anthranyl methyl
15	9-[10-chloro]anthranyl methyl
16	2-benzthienylmethyl
35	4-[4-hydroxyphenyl]benzyl
17	4-[4-octylphenyl]benzyl
18	4-[4-pentylphenyl]benzyl
40	4-[4-octyloxyphenyl]benzyl
19	3-pyridylmethyl
20	5-nitro-1-naphthylmethyl
21	4-pyridylmethyl
22	4-quinolylmethyl
23	3-quinolylmethyl
45	4-stilbenyl
24	2-quinolylmethyl
25	2-pyridylmethyl
26	2-fluorenylmethyl
50	4-phenoxyphenethyl
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TABLE 2A

COMPOUND NO.	SIDECHAIN
34	4-[4-pentylcyclohexyl]benzyl
35	4-benzylphenethyl
36	4-[4-biphenyl]benzyl
37	4-trifluoromethylbenzyl
38	trans-cinnamyl
39	4-[1-oxa]fluorenylmethyl
40	4-[4-pentoxyphenyl]benzyl
41	4-thiomethylbenzyl
42	2,3-[2-methyl-3-[4-t-butylphenyl]]propenyl
43	9-(1-methyl)-acridinylmethyl
44	2-hydroxy-1-naphthylmethyl
45	4-[2-phenyl-6-methoxy]quinoylmethyl
46	4-diphenylmethylbenzyl
47	3,4 cyclohexenylmethyl
48	3,4-methylenedioxybenzyl
49	3-phenoxybenzyl
50	4-benzylbenzyl
51	3-benzylxy-6-methoxy benzyl
52	4-benzylxy-3-methoxybenzyl
53	3,4-dibenzylxybenzyl
54	4-[4-methoxyphenyl]benzyl
55	4-[3-cyanopropoxy]benzyl
56	3,4-ethylenedioxybenzyl
57	4-[4-nitrophenoxy]benzyl
58	2,3-methylenedioxybenzyl
59	2-benzylxyphenethyl
60	2-ethoxy-1-naphthylmethyl
61	2-benzylfurylmethyl
62	3-phenoxyphenethyl
63	4-phenoxyphenethyl
64	4-[4-nitrophenyl]benzyl
65	6-methoxy-2-naphthylmethyl
66	3-methyl-5-thienylmethyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
67	5-phenyl-2-thienylmethyl
68	4-benzylxyphenethyl
69	3-benzylxyphenethyl
70	4-[2-nitrophenoxy]benzyl
71	5-[4-methoxyphenyl]-2-thienylmethyl
72	4-difluormethoxybenzyl
73	2,3,4,5,6-pentamethylbenzyl
74	5-iodo-2-thienylmethyl
75	4-[2-(2-chloroethoxy)ethoxy]benzyl
76	3,4-dimethylbenzyl
77	3-acetoxybenzyl
78	4-nitrobenzyl
79	4-phenylethynylbenzyl
80	4-[2-chloro-6-fluorobenzyl]benzyl
81	4-[3,4-dichlorophenoxy]benzyl
82	5-[2,3-dihydrobenzfuryl]methyl
83	4-[2-(N,N-diethylamino)ethoxy]benzyl
84	2-bicyclo[2.1.2]heptylmethyl
85	2-hydroxy-5-phenylbenzyl
86	3-[4-chlorophenoxy]benzyl
87	4-[3-chlorophenoxy]-3-nitrobenzyl
88	4-[2-chlorophenoxy]-3-nitrobenzyl
89	3,5-dimethylbenzyl
90	4-[4-ethylphenyl]benzyl
91	3-phenylbenzyl
92	4-[3-fluorophenyl]benzyl
93	4-[4-chlorobenzyl]benzyl
94	4-[4-chlorophenoxy]-3-nitrobenzyl
95	4-[4-methylphenoxy]benzyl
96	4-[4-t-butylphenoxy]benzyl
97	4-[4-methylphenyl]benzyl
98	4-[4-methoxyphenoxy]benzyl
99	4-acetoxy-3-methoxybenzyl

TABLE 2A

5	COMPOUND NO.	SIDECHAIN
100	100	4-[ (2-phenyl)ethyl]benzyl
101	101	3-[5-phenyl]pyridinylmethyl
102	102	4-[2-nitrophenyl]benzyl
103	103	2-[1-hydroxy]fluorenylmethyl
104	104	4-benzyl-3-methoxybenzyl
105	105	4-[cyclohexylmethoxy]-3-ethoxybenzyl
106	106	3-[3,3'-dichlorophenoxy]benzyl
107	107	4-[4-propylphenyl]benzyl
108	108	4-thiophenylbenzyl
109	109	4-[alpha-hydroxybenzyl]benzyl
110	110	2,2-dinitro-4-thiophenebenzyl
111	111	3-[3-trifluoromethylphenoxy]benzyl
112	112	4-[t-butylethynyl]benzyl
113	113	4-phenoxy-3-methoxy-benzyl
114	114	4-[3-trifluoromethylphenoxy]-3-nitrobenzyl
115	115	2-phenylthiobenzyl
116	116	2-[4-chlorophenyl]-6-benzoxazolemethyl
117	117	4-[alpha-methoxybenzyl]benzyl
118	118	4-cyclohexylbenzyl
119	119	3-[3,4-dichlorophenoxy]benzyl
120	120	acenaphthlenylmethyl
121	121	4-[1,1,2,2-tetrafluoroethoxy]benzyl
122	122	4-benzoyloxy-3,3'-dimethoxybenzyl
123	123	3-[cyclohexylmethoxy]benzyl
124	124	4-cyclohexyloxybenzyl
125	125	3-[2-quinoylmethoxy]benzyl
126	126	4-[alpha-ethoxybenzyl]benzyl
127	127	4-[cyclohexylethoxy]benzyl
128	128	4-[alpha-propoxybenzyl]benzyl
129	129	4-[4-methyl-1-piperidino]benzyl
130	130	2-thiophene-1,2-cyclohexenylmethyl
131	131	4-[4-nitrobenzyl]benzyl
132	132	3-[4-trifluoromethylphenoxy]benzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
133	3-benzoyl-2,4-dichlorobenzyl
134	4-[2-(2-thiopropyl)ethoxy]benzyl
135	4-[2-methyl-1-piperidino]benzyl
136	4-hydroxybenzyl
137	4-(2-pyridyl)benzyl
138	4-acetoxybenzyl
139	5,6-benzenorbornylmethyl
140	3-phenylcyclopentylmethyl
141	1-adamantylmethyl
142	3-[cyclohexylmethoxy]-4-methoxybenzyl
143	2-[2-glucosyl]benzyl
144	4-[4-pentoxybiphenyl]benzyl
145	3,4-dihydroxybenzyl
146	4-[4-methylpiperazino]benzyl
147	4-morpholinobenzyl
148	4-[4-chlorophenylsulfonyl]benzyl
149	4-methylsulfonyloxybenzyl
150	4-benzoyloxybenzyl
151	5-phenyl-3-pyridinylmethyl
152	4-[N,N-bis(2-chloroethyl)amino]benzyl
153	3-cyclohexyloxybenzyl
154	4-[2-t-butoxyethoxy]benzyl
155	3,3'-dichloro-4-hydroxy-benzyl
156	1,2,3,4,-tetrahydro-9-anthranyl methyl
157	4-cyclohexanoyloxybenzyl
158	4-nanonoyloxybenzyl
159	4-[phenylsulfinyl]benzyl
160	4-anilinobenzyl
161	cyclohexylmethyl
162	3-benzoyloxybenzyl
163	3-nanonoyloxybenzyl
164	4-[cyclohexyl]cyclohexylmethyl
165	3-cyclohexanoyloxybenzyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
166	4-[cyclohexanoyloxy]-3,3'-(dimethoxy)benzyl
167	4-[nonanoyloxy]-3,3'-(dimethoxy)benzyl
168	1,2,3,4-tetrahydro-6-naphthylmethyl
169	2-hydroxybenzyl
170	[2-{6,6-dimethyl-bicyclo[3.1.1]hept-2-enyl}methyl
171	1-cyclohexenyl-4-isopropylmethyl
172	4-[4-methoxyphenyl]butyl
173	4-[(2,3,4,5,6-pentamethyl)phenylsulfonyloxy]benzyl
174	4-[1-pyrrolidinosulfonyl]benzyl
175	3-[4-methoxyphenyl]propyl
176	8-phenyloctyl
177	4-[2,3-dihydroxypropoxy]benzyl
178	4-[N-methylanilino]benzyl
179	2-[2-naphthyl]ethyl
189	6-methyl-2-naphthylmethyl
190	cis-bicyclo[3.3.0]octane-2-methyl
191	2-tridecynyl
192	4-butyl-2-cyclohexylmethyl
193	4-[(4-fluorobenzoyl)amino]benzyl
194	4-[(3-fluorobenzoyl)amino]benzyl
195	8-phenoxyoctyl
196	6-phenylhexyl
197	10-phenyldecyl
198	8-bromoocetyl
199	11-tridecynyl
200	8-[4-methoxyphenoxy]octyl
201	8-[4-phenylphenoxy]octyl
202	8-[4-phenoxyphenoxy]octyl
203	3-[3-trifluoromethylphenoxy]benzyl
204	10-undecenyl
205	4-cyclohexylbutyl
206	4-phenyl-2-fluorobenzyl
207	7-hexadecynyl

TABLE 2A

COMPOUND NO.	SIDECHAIN
208	3-[cyclopentyl]propyl
209	4-[2-methylphenyl]benzyl
210	4-[phenylazo]benzyl
211	4-[4-fluorophenyl]benzyl
212	3-nitro-4-[4-nitrophenyl]benzyl
213	3-nitro-4-[2-nitrophenyl]benzyl
214	9-deceny1
215	4-[3,4-dimethoxyphenyl]benzyl
216	4-(4-trifluoromethylphenyl)benzyl
217	5-hexenyl
218	4-[2-thienyl]benzyl
219	4-[6-phenylhexyloxy]benzyl
220	9,10-dihydro-2-phenanthrene methyl
221	4-[3,4-dimethylphenyl]benzyl
222	4-[4-methylphenyl]-2-methylbenzyl
223	4-[3-phenylpropyloxy]benzyl
224	4-[3-methylphenyl]benzyl
225	4-[4-methylphenyl]-3-methylbenzyl
226	4-[4-pentenyloxy]benzyl
227	4-[1-heptynyl]benzyl
228	3-[4-t-butyl-phenylthio]benzyl
229	4-[4-chlorophenyl]benzyl
230	4-[4-bromophenyl]benzyl
231	4-[4-cyanophenyl]benzyl
232	4-[1-nonynyl]benzyl
233	4-[11-tridecynyoxy]benzyl
234	12-phenyldodecyl
235	6-phenyl-5-hexynyl
236	11-phenyl-10-undecynyl
237	4-[2-methylphenyl]-3-methylbenzyl
238	3-[2'-thienyl]-2-thienylmethyl
239	4-[benzyloxymethyl]cyclohexylmethyl
240	4-[4-chlorophenoxy]benzyl

TABLE 2A

5	COMPOUND NO.	SIDECHAIN
	241	4-[benzyl]cyclohexylmethyl
	242	4-benzoylbenzyl
10	243	4-[phenoxyethyl]benzyl
	244	4-[4-chlorobenzyl]benzyl

TABLE 2B

15	COMPOUND NO.	GLYCOPEPTIDE CORE	SIDECHAIN
20	180	vancomycin	1-naphthylmethyl
	181	vancomycin	4-phenylbenzyl
	182	A82846A	4-phenylbenzyl
	183	A82846C	4-phenylbenzyl
25	184	A82846C	4-phenoxybenzyl
	185	PA-42867 A	4-phenylbenzyl
	186	reduced A838450A	4-phenylbenzyl
	187	alpha-avoparcin	4-phenylbenzyl
	188	beta-avoparcin	4-phenylbenzyl

30        The formula I compounds have in vitro and in vivo activity against Gram-positive pathogenic bacteria. The minimal inhibitory concentrations (MIC) at which the formula I compounds inhibit certain bacteria are given in Table 3. The MIC's were determined using a standard broth micro-dilution assay.

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TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	vancamycin	A82846A	A82846B	A82846C	1	2	3	4	5	6
Staphylococcus aureus 446	0.5	0.25	0.25	0.5	≤0.06	≤0.06	≤0.06	1	0.5	
Staphylococcus aureus 489	0.125	0.5	≤0.06	≤0.06	0.25	≤0.06	≤0.06	0.5	0.25	
Staphylococcus aureus 447	0.5	0.25	0.25	0.5	≤0.06	≤0.06	≤0.06	0.5	0.5	
Staphylococcus aureus X400	0.5	0.125	0.125	0.25	≤0.06	≤0.06	≤0.06	0.25	0.5	
Staphylococcus aureus X778	0.5	0.125	0.125	0.5	0.125	≤0.06	≤0.06	0.5	0.5	
Staphylococcus aureus 491	1	0.25	0.25	1	2	≤0.06	0.5	≤0.06	0.5	
Staphylococcus aureus S13E	0.5	0.125	0.125	0.25	0.125	≤0.06	≤0.06	≤0.06	1	0.25
Staphylococcus aureus SA1199	0.5	0.125	0.125	0.25	≤0.06	0.5	0.125	≤0.06	1	0.25
Staphylococcus aureus SA1199A	0.125	\$0.06	\$0.06	0.125	\$0.06	\$0.06	\$0.06	0.5	0.25	
Staphylococcus aureus SA1199B	0.5	\$0.06	0.125	\$0.06	—	\$0.06	\$0.06	\$0.06	\$0.06	
Staphylococcus haemolyticus 105	16	0.5	1	1	4	2	4	0.5	2	0.5
Staphylococcus haemolyticus 415	8	1	4	2	4	1	8	0.5	1	0.5
Staphylococcus epidermidis 270	16	0.25	0.25	0.125	8	8	8	≤0.06	≤0.06	
Enterococcus faecium 180	>64	16	8	16	0.5	0.25	0.5	0.125	≤0.06	
Enterococcus faecium 180-1	0.5	0.125	0.125	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	
Enterococcus faecalis 2041	2	0.125	0.25	0.5	0.125	0.125	≤0.06	≤0.06	≤0.06	
Enterococcus faecalis 276	1	0.125	0.125	0.5	≤0.06	0.5	≤0.06	≤0.06	≤0.06	
Enterococcus gallinarum 245	4	0.125	0.25	0.5	4	≤0.06	≤0.06	≤0.06	≤0.06	
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	0.5	—	0.125	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	
Streptococcus pneumoniae P1	0.25	—	—	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	7	8	9	10	11	12	13	14	15	16	17
Staphylococcus aureus 446	8	2	2	16	4	32	2	4	1	4	2
Staphylococcus aureus 489	2	4	0.5	>64	1	8	1	2	≤0.06	0.5	1
Staphylococcus aureus 447	4	8	4	>64	4	32	8	8	2	4	8
Staphylococcus aureus X400	1	8	0.5	>64	0.5	8	1	4	0.25	0.5	0.5
Staphylococcus aureus X778	0.25	8	0.25	16	0.25	8	2	4	0.25	2	0.5
Staphylococcus aureus 491	2	4	0.5	16	1	4	2	1	0.25	1	2
Staphylococcus aureus S13E	2	8	0.5	8	0.5	8	0.25	4	0.5	1	1
Staphylococcus aureus SA1199	4	2	0.25	8	2	8	0.5	8	0.25	2	4
Staphylococcus aureus SA1199A	≤0.06	2	≤0.06	4	≤0.06	8	≤0.06	0.5	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	1		0.25	8	2	4	8	0.25	1	1	1
Staphylococcus haemolyticus 105	8	8	4	>64	4	16	8	4	0.5	8	8
Staphylococcus haemolyticus 415	16	8	4	>64	2	32	1	8	2	4	8
Staphylococcus epidermidis 270	4	16	>64	2	0.125	8	4	1	0.5	1	2
Enterococcus faecium 180	2	1	1	8	1	4	2	1	0.5	1	2
Enterococcus faecium 180-1	≤0.06	0.5	≤0.06	4	≤0.06	4	≤0.06	1	≤0.06	0.125	≤0.06
Enterococcus faecalis 2041	0.125	4	0.25	16	0.5	16	0.125	2	≤0.06	0.5	0.25
Enterococcus faecalis 276	1	4	0.26	18	1	4	0.5	4	≤0.06	2	0.5
Enterococcus gallinarum 245	0.5	8	0.25	8	≤0.06	32	0.25	0.25	≤0.06	1	0.5
Haemophilus influenzae RD	16	>64	≤0.06	64	32						32
Escherichia coli EC14	>64	>64	>64	>64	>64						>64
Streptococcus Pyogenes C203	≤0.06	≤0.06	0.5	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	18	19	20	21	22	23	24	25	26	27	28
Staphylococcus aureus 446	2	0.5	0.5	>64	16	38	0.5	0.5	0.25	2	0.25
Staphylococcus aureus 489	1	0.25	0.5	32	8	>64	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus 447	8	1	4	>64	16	-	1	0.25	2	8	1
Staphylococcus aureus X400	1	0.25	0.5	32	8	16	0.25	≤0.06	0.25	0.5	≤0.06
Staphylococcus aureus X778	0.5	0.25	0.25	32	8	16	0.125	≤0.06	0.125	0.5	≤0.06
Staphylococcus aureus 491	2	2	1	64	8	16	0.5	0.125	0.5	1	0.25
Staphylococcus aureus S13E	1	≤0.06	≤0.06	64	16	16	≤0.06	≤0.06	0.25	0.125	≤0.06
Staphylococcus aureus SA1199	2	0.5	2	64	16	16	0.5	≤0.06	1	0.5	0.125
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	16	4	16	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	2	1	0.5	64	16	16	2	0.125	0.5	1	0.125
Staphylococcus haemolyticus 105	16	4	8	>64	16	4	4	1	4	16	4
Staphylococcus haemolyticus 415	8	8	4	64	16	16	≤0.06	32	8	8	8
Staphylococcus epidermidis 270	8	2	2	32	4	64	1	0.5	1	4	1
Enterococcus faecium 180	2	1	1	8	1	>64	4	0.5	4	8	1
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	8	≤0.06	32	≤0.06	≤0.06	0.25	0.5	≤0.06
Enterococcus faecalis 2041	0.25	≤0.06	≤0.06	32	2	32	≤0.06	0.25	0.25	0.125	0.25
Enterococcus faecalis 276	1	≤0.06	0.25	64	4	32	0.25	0.25	≤0.06	0.5	≤0.06
Enterococcus gallinarum 245	1	≤0.06	0.25	8	1	8	0.25	≤0.06	0.125	0.5	0.25
Haemophilus influenzae RD	16	32	8	>64	64	>64	>64	32	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	2	≤0.06	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	0.5	0.25	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	29	30	31	32	33	34	35	36	37	38	39
Staphylococcus aureus 446	1	1	0.5	1	4	32	0.5	8	0.5	0.5	0.125
Staphylococcus aureus 489	1	0.125	≤0.06	1	≤0.06	8	≤0.06	2	0.125	≤0.06	≤0.06
Staphylococcus aureus 447	0.25	2	0.5	0.5	0.125	8	0.125	2	0.125	0.125	0.25
Staphylococcus aureus X400	0.25	≤0.06	0.125	0.5	0.25	32	0.25	4	0.25	1	≤0.06
Staphylococcus aureus X778	≤0.06	≤0.06	0.125	0.5	0.5	16	≤0.06	2	≤0.06	0.5	≤0.06
Staphylococcus aureus 491	0.25	0.5	0.5	0.25	0.125	8	0.125	1	0.25	0.5	0.25
Staphylococcus aureus S13E	1	0.125	0.25	1	≤0.06	16	≤0.06	2	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199	0.25	0.5	0.25	1	1	16	0.25	4	0.25	1	≤0.06
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.25	0.125	0.25	0.125	0.125	16	0.25	4	≤0.06	0.125	≤0.06
Staphylococcus haemolyticus 105	4	4	4	4	2	32	2	4	0.25	1	2
Staphylococcus haemolyticus 415	1	16	16	4	8	>64	4	8	1	1	4
Staphylococcus epidermidis 270	0.5	2	1	1	2	16	1	2	0.25	0.5	0.25
Enterococcus faecium 180	0.25	2	4	0.25	2	4	1	0.25	0.125	0.125	0.125
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	0.25	≤0.06	0.25	0.25	≤0.06	8	≤0.06	1	0.125	≤0.06	≤0.06
Enterococcus faecalis 276	0.25	0.25	0.25	0.125	≤0.06	16	≤0.06	2	1	0.5	≤0.06
Enterococcus gallinarum 245	0.25	≤0.06	0.25	0.25	0.25	4	≤0.06	0.25	0.125	0.125	≤0.06
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	64	>64	32	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	-	-	-	-	-	-	-	-	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	-	-	-	-	-	-	-	-	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	40	41	42	43	44	45	46	47	48	49	50
Staphylococcus aureus 446	4	2	1	0.5	0.25	1	1	0.125	0.125	0.5	0.5
Staphylococcus aureus 489	4	\$0.06	0.5	\$0.06	\$0.06	0.5	1	\$0.06	\$0.06	\$0.06	\$0.06
Staphylococcus aureus 447	2	0.25	0.5	2	1	1.6	2	2	2	1	0.5
Staphylococcus aureus Y400	4	\$0.06	1	0.25	0.06	0.25	2	\$0.06	\$0.06	0.125	0.125
Staphylococcus aureus X778	4	0.125	1	\$0.06	\$0.06	0.25	2	\$0.06	\$0.06	\$0.06	0.125
Staphylococcus aureus 491	4	0.5	0.5	1	0.125	1	2	0.5	0.25	0.125	0.5
Staphylococcus aureus S13E	4	\$0.06	0.5	0.25	0.25	0.5	2	\$0.06	\$0.06	\$0.06	0.125
Staphylococcus aureus SA1199	4	\$0.06	1	0.5	0.25	2	2	0.5	0.25	2	1
Staphylococcus aureus SA1199A	0.5	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.5	0.25	\$0.06	\$0.06	\$0.06
Staphylococcus aureus SA1199B	8	0.25	2	0.5	0.25	1	2	0.25	1	1	2
Staphylococcus haemolyticus 105	2	2	4	2	1.6	2	4	2	1	1	0.5
Staphylococcus haemolyticus 415	2	4	1	8	4	8	2	16	8	1	1
Staphylococcus epidermidis 270	1	0.25	0.5	2	0.5	8	2	1	1	1	0.5
Enterococcus faecium 180	1	0.25	0.25	4	8	1	0.5	2	1	0.25	0.25
Enterococcus faecium 180-1	2	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	1	\$0.06	0.125	0.5	\$0.06	0.125	1	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 276	2	\$0.06	8	0.5	0.125	0.25	0.5	\$0.06	\$0.06	0.25	0.25
Enterococcus gallinarum 245	11	\$0.06	1	0.5	0.5	0.5	0.25	16	1	1	1
Haemophilus influenzae RD					>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	51	52	53	54	55	56	57	58	59	60	61
Staphylococcus aureus 446	0.25	\$0.06	2	1	0.5	0.5	0.25	0.25	0.5	1	0.5
Staphylococcus aureus 489	\$0.06	0.5	2	\$0.06	1	1	0.5	\$0.06	0.125	0.5	1
Staphylococcus aureus 447	0.5	\$0.06	4	0.25	4	2	0.5	1	1	2	2
Staphylococcus aureus X400	\$0.06	\$0.06	4	\$0.06	\$0.06	\$0.06	0.125	\$0.06	0.25	0.5	\$0.06
Staphylococcus aureus X778	0.5	0.5	2	\$0.06	0.5	0.125	\$0.06	\$0.06	\$0.06	0.25	0.125
Staphylococcus aureus 491	0.25		2		0.5	0.5		0.125		1	0.5
Staphylococcus aureus S13E	0.5	0.5	2	0.5	0.5	0.125	\$0.06	\$0.06	0.125	0.25	0.125
Staphylococcus aureus SA1199	0.5	2	2	0.5	0.5	0.5	1	1	\$0.06	0.5	0.25
Staphylococcus aureus SA1199A	\$0.06	\$0.06	1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Staphylococcus aureus SA1199B	1	2	2	1	0.5	0.5	0.125	0.125	0.5	0.5	0.25
Staphylococcus haemolyticus 105	0.5	0.5	2	2	4	4	8	4	8	>64	64
Staphylococcus haemolyticus 415	1	1	2	1	16	16	1	8	8	16	8
Staphylococcus epidermidis 270	0.5	0.5	2	0.25	1	1	0.5	4	1	2	1
Enterococcus faecium 180	0.5	2	1	1	2	2	0.5	8	8	4	2
Enterococcus faecium 180-1	\$0.06	\$0.06	2	\$0.06	\$0.06	\$0.06	0.25	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	\$0.06	0.5	1	\$0.06	0.125	0.25	\$0.06	0.5	0.5	0.25	\$0.06
Enterococcus faecalis 276	\$0.06	0.125	8	1	0.5	0.25	0.5	0.5	0.125	0.5	0.25
Enterococcus gallinarum 245	1	1	2	0.5	16	16	2	0.5	1	16	8
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	62	63	64	65	66	67	68	69	70	71	72
Staphylococcus aureus 446	2	0.5	0.25	2	0.25	0.25	0.125	1	0.125	4	2
Staphylococcus aureus 489	2	8	0.25	0.125	1	\$0.06	0.125	0.25	\$0.06	0.25	\$0.06
Staphylococcus aureus 447	0.5	1	0.5	1	1	1	0.25	1	0.5	4	1
Staphylococcus aureus X400	\$0.06	\$0.06	0.125	0.125	0.125	1	\$0.06	0.5	\$0.06	1	0.125
Staphylococcus aureus X778	0.5	0.125	2	0.5	\$0.06	0.25	\$0.06	0.125	\$0.06	2	0.25
Staphylococcus aureus 491	0.125	0.5	0.125	0.5	0.25	1	0.125	1	0.5	2	0.25
Staphylococcus aureus S13E	0.5	0.125	2	0.5	\$0.06	0.25	\$0.06	0.25	\$0.06	1	\$0.06
Staphylococcus aureus SA1199	0.25	0.25	1	0.5	0.25	1	\$0.06	1	\$0.06	1	1
Staphylococcus aureus SA1199A	\$0.06	0.125	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.25	\$0.06
Staphylococcus aureus SA1199B	1	0.5	0.125	2	0.25	1	0.5	2	\$0.06	4	\$0.06
Staphylococcus haemolyticus 105	2	4	64	64	64	64	2	4	2	16	1
Staphylococcus haemolyticus 415	4	8	2	4	8	2	4	8	2	8	4
Staphylococcus epidermidis 270	1	1	0.5	1	1	0.5	2	2	0.25	2	0.25
Enterococcus faecium 180	4	16	0.125	0.5	2	0.25	2	4	0.5	4	0.5
Enterococcus faecium 180-1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.25	\$0.06
Enterococcus faecalis 2041	\$0.06	0.25	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	1	\$0.06
Enterococcus faecalis 276	0.5	0.5	0.5	0.5	0.5	\$0.06	\$0.06	0.5	\$0.06	2	\$0.06
Enterococcus gallinarum 245	4	8	2	4	8	2	4	8	2	8	4
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	32
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	73	74	75	76	77	78	79	80	81	82	83
Staphylococcus aureus 446	0.25	4	0.25	0.25	0.06	2	2	4	2	2	1
Staphylococcus aureus 489	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	2	2	2	0.25	0.25
Staphylococcus aureus 447	0.25	1	1	0.5	1	≤0.06	2	2	2	4	2
Staphylococcus aureus X400	0.5	≤0.06	≤0.06	0.25	≤0.06	≤0.06	0.25	4	1	0.25	2
Staphylococcus aureus X778	1	≤0.06	≤0.06	0.25	≤0.06	≤0.06	2	0.5	1	0.5	0.5
Staphylococcus aureus 491	0.25	0.125	0.25	0.25	0.25	0.25	4	1	1	1	0.5
Staphylococcus aureus S13E	0	0	0	0	0.125	0.125	4	1	0.5	≤0.06	0.125
Staphylococcus aureus SAL199	0.5	≤0.06	2	≤0.06	≤0.06	0.125	1	2	2	0.25	2
Staphylococcus aureus SAL199A	0.25	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.125	1	0.5	0.5	0.25
Staphylococcus aureus SAL199B	≤0.06	1	0.5	0.25	0.125	≤0.06	1	1	1	1	1
Staphylococcus haemolyticus 105	0.5	4	2	2	2	2	4	4	1	8	2
Staphylococcus haemolyticus 415	2	4	4	8	8	16	4	4	4	8	4
Staphylococcus epidermidis 270	0.125	0.5	0.25	0.5	0.5	0.5	0.5	2	1	4	2
Enterococcus faecium 180	0.5	0.5	0.5	0.5	8	1	≤0.06	0.125	50.06	2	8
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	50.06	0.125	0.125	0.125
Enterococcus faecalis 2041	0.125	≤0.06	≤0.06	0.25	≤0.06	≤0.06	50.06	50.06	50.06	0.5	0.5
Enterococcus faecalis 276	0.25	≤0.06	≤0.06	0.25	0.125	0.125	50.06	50.06	50.06	50.06	50.06
Enterococcus gallinarum 245	2	≤0.06	4	4	0.25	0.125	50.06	50.06	0.25	0.125	0.5
Hemophilus influenzae RD	0.25	0.5	2	>64	64	16	16	16	64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	84	85	86	87	88	89	90	91	92	93	94
Staphylococcus aureus 446	0.5	0.125	1	1	0.25	0.5	2	0.5	2	2	1
Staphylococcus aureus 489	\$0.06	0.25	1	0.5	0.5	0.25	2	\$0.06	\$0.06	0.25	2
Staphylococcus aureus 447	4	0.125	0.5	0.5	0.25	1	1	0.5	0.5	0.25	0.5
Staphylococcus aureus X400	\$0.06	0.25	1	1	\$0.06	0.25	1	0.5	0.5	\$0.06	1
Staphylococcus aureus X778	\$0.06	0.25	1	2	0.5	0.25	1	\$0.06	0.25	1	0.5
Staphylococcus aureus 491	1	0.125	1	2	0.5	1	2	1	1	0.25	0.5
Staphylococcus aureus S13E	0.125	0.5	1	0.5	1	0.25	1	\$0.06	0.125	1	2
Staphylococcus aureus S1199	0.25	0.5	2	1	0.5	2	1	\$0.06	1	2	0.5
Staphylococcus aureus S1199A	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.5	\$0.06	\$0.06	\$0.06	\$0.06
Staphylococcus aureus S1199B	0.5	1	1	0.5	1	1	1	0.5	0.5	1	2
Staphylococcus haemolyticus 105	8	1	1	1	1	1	1	2	2	1	2
Staphylococcus haemolyticus 415	16	2	1	2	2	2	2	2	2	1	2
Staphylococcus epidermidis 270	1	0.5	1	1	1	1	1	0.5	1	1	1
Enterococcus faecium 180	4	\$0.06	\$0.06	\$0.06	\$0.125	0.125	0.25	0.5	0.125	\$0.06	0.25
Enterococcus faecium 180-1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.125	\$0.06	0.125	\$0.06	\$0.06
Enterococcus faecalis 276											
Enterococcus gallinarum 245	0.25	2	1	2	\$0.06	\$0.06	2	2	2	1	2
Haemophilus influenzae RD											
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	95	96	97	98	99	100	101	102	103	104	105
Staphylococcus aureus 446	0.5	1	0.5	0.5	0.5	1	0.5	1	0.5	≤0.06	0.25
Staphylococcus aureus 489	2	1	0.25	≤0.06	0.25	0.5	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Staphylococcus aureus 447	0.5	1	1	0.25	2	0.5	1	1	1	0.25	0.5
Staphylococcus aureus X400	1	2	1	≤0.06	0.125	1	≤0.06	≤0.06	≤0.06	≤0.06	0.5
Staphylococcus aureus X778	1	1	0.25	≤0.06	0.5	1	0.25	≤0.06	0.5	≤0.06	0.5
Staphylococcus aureus 491	1	1	0.5	0.25	1	≤0.06	0.5	1	1	≤0.06	0.25
Staphylococcus aureus S13E	2	1	>64	0.5	0.5	1	0.25	1	1	≤0.06	0.5
Staphylococcus aureus SA1199	0.5	2	2	0.5	0.5	0.5	0.25	0.125	1	2	1
Staphylococcus aureus SA1199A	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	0.5	≤0.06	≤0.06	≤0.06	0.25
Staphylococcus aureus SA1199B	1	1	1	1	0.5	0.5	1	1	2	0.125	0.5
Staphylococcus haemolyticus 105	1	2	2	1	8	1	1	2	4	2	1
Staphylococcus haemolyticus 415	1	2	2	1	32	2	8	4	8	2	1
Staphylococcus epidermidis 270	1	2	1	≤0.06	1	0.5	0.5	1	1	0.25	0.25
Enterococcus faecium 180	0.5	0.5								≤0.06	0.25
Enterococcus faecium 180-1	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	≤0.06	1	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25
Enterococcus faecalis 276	0.125	0.5	≤0.06	0.125	0.25	0.25	0.125	0.25	0.25	≤0.06	0.25
Enterococcus gallinarum 245	1	2	2	1	32	2	8	4	8	2	1
Haemophilus influenzae RD						>64	>64	>64	>64	32	64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	106	107	108	109	110	111	112	113	114	115	116
Staphylococcus aureus 446	2	2	1	0.5	2	2	50.06	0.5	0.125	0.5	0.5
Staphylococcus aureus 489	2	0.25	50.06	1	1	0.25	0.125	1	0.125	1	1
Staphylococcus aureus 447	0.25	1	0.5	1	1	1	0.25	0.5	0.5	0.5	1
Staphylococcus aureus X400	1	1	2	50.06	1	1	0.125	2	1	1	1
Staphylococcus aureus X778	1	0.5	0.125	50.06	0.5	2	1	1	1	2	1
Staphylococcus aureus 491	0.5	1	0.25	0.25	0.25	2	1	0.25	1	0.5	0.5
Staphylococcus aureus S13E	1	2	1	0.25	1	1	50.06	2	0.25	1	1
Staphylococcus aureus SA1199	1	1	2	50.06	0.25	2	2	1	2	0.125	4
Staphylococcus au... s SA1199A	50.06	50.06	50.06	50.06	50.06	0.5	0.125	50.06	50.06	50.06	50.06
Staphylococcus aureus SA1199B	2	2	0.5	0.5	1	0.5	50.06	1	0.25	0.5	0.5
Staphylococcus haemolyticus 105	1	2	2	1	4	1	2	4	2	1	2
Staphylococcus haemolyticus 415	1	2	1	4	2	4	1	2	1	2	4
Staphylococcus epidermidis 270	0.25	0.5	0.125	0.25	0.25	1	1	0.25	1	0.5	1
Enterococcus faecium 180	50.06	0.125	0.125	0.25	0.25	50.06	50.06	50.06	50.06	50.06	50.06
Enterococcus faecium 180-1	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06
Enterococcus faecalis 2041	0.125	0.5	50.06	50.06	50.06	50.06	50.06	50.06	0.25	50.06	50.06
Enterococcus faecalis 276	0.5	1	0.5	50.06	0.5	0.5	0.5	0.25	1	0.125	0.25
Enterococcus gallinarum 245	1	2	50.06	50.06	2	4	2	1	2	2	4
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus Pyogenes C203	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06
streptococcus pneumoniae P1	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

	Organism	117	118	119	120	121	122	123	124	125	126	127
staphylococcus aureus 446	0.5	1	2	2	2	1	2	4	4	2	1	1
staphylococcus aureus 489	0.125	0.25	0.5	2	1	≤0.06	2	0.25	2	0.25	2	2
staphylococcus aureus 447	0.5	0.25	2	1	0.5	0.25	1	0.25	2	1	2	2
staphylococcus aureus X400	\$0.06	0.25	1	0.25	0.125	≤0.06	1	1	1	1	1	2
staphylococcus aureus X778	0.25	0.5	2	0.125	0.5	≤0.06	1	0.5	2	0.5	1	1
staphylococcus aureus 491	0.5	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.125	1	0.25	1
staphylococcus aureus S13E	\$0.06	0.25	0.25	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	1	0.5	2
staphylococcus aureus SAI199	\$0.06	2	2	1	1	≤0.06	2	1	0.5	0.125	2	2
staphylococcus aureus SAI199A	\$0.06	\$0.06	0.25	\$0.06	\$0.06	\$0.06	0.125	\$0.06	\$0.06	0.25	0.25	0.25
staphylococcus aureus SAI199B	0.5	\$0.06	0.5	0.125	0.25	\$0.06	0.5	\$0.06	2	1	1	2
staphylococcus haemolyticus 105	1	1	2	2	2	1	2	2	4	0.5	2	2
staphylococcus haemolyticus 415	2	1	2	2	2	1	1	1	1	2	2	4
staphylococcus epidermidis 270	0.5	1	2	2	1	≤0.06	1	0.25	1	1	1	1
Enterococcus faecium 180	1	0.125	0.125	\$0.06	\$0.06	\$0.06	0.25	\$0.06	1	1	1	1
Enterococcus faecium 180-1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	≤0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	≤0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 276	0.25	\$0.06	0.125	\$0.06	\$0.06	\$0.06	≤0.06	\$0.06	\$0.06	2	1	1
Enterococcus gallinarum 245	2	1	2	2	2	1	1	1	1	12	2	4
Haemophilus influenzae RD	16	16	16	16	16	16	16	16	16	16	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

Organism	128	129	130	131	132	133	134	135	136	137	138
Staphylococcus aureus 446	4	2	1	2	1	2	2	1	50.06	0.25	0.125
Staphylococcus aureus 489	1	50.06	0.5	1	1	0.5	0.5	0.125	50.06	50.06	50.06
Staphylococcus aureus 447	1	1	1	1	2	1	1	1	2	4	2
Staphylococcus aureus X400	1	0.25	0.5	1	1	0.5	0.25	50.06	50.06	50.06	50.06
Staphylococcus aureus X778	1	0.25	1	0.5	2	2	1	1	50.06	50.06	0.25
Staphylococcus aureus 491	2	0.5	0.5	0.125	0.5	0.25	0.5	0.25	0.25	0.25	0.125
Staphylococcus aureus S13E	1	0.25	0.5	1	2	1	2	1	50.06	50.06	50.06
Staphylococcus aureus SA1199	0.5	0.25	1	0.25	1	0.25	0.25	1	50.06	50.06	50.06
Staphylococcus aureus SA1199A	0.5	50.06	50.06	0.25	0.25	0.25	0.25	50.06	50.06	50.06	50.06
Staphylococcus aureus SA1199B	2	0.25	2	1	2	2	2	0.25	50.06	50.06	50.06
Staphylococcus haemolyticus 105	1	4	1	1	1	2	2	0.5	2	2	0.5
Staphylococcus haemolyticus 415	2	4	2	2	2	2	4	2	4	4	8
Staphylococcus epidermidis 270	1	1	1	1	2	1	2	0.5	1	0.5	2
Enterococcus faecium 180	1	4	1	50.06	0.25	1	0.5	1	2	0.125	4
Enterococcus faecium 180-1	0.125	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06	50.06
Enterococcus faecalis 2041	0.5	50.06	0.125	50.06	1	0.25	0.25	0.125	50.06	50.06	50.06
Enterococcus faecalis 276	1	0.125	1	0.25	1	1	1	0.5	50.06	50.06	50.06
Enterococcus gallinarum 245	2	0.125	2	2	2	2	4	2	4	8	0.125
Haemophilus influenzae RD	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

Organism	139	140	141	142	143	144	145	146	147	148	149
Staphylococcus aureus 446	0.5	0.125	2	0.5	16	0.5	0.5	0.5	1	0.5	
Staphylococcus aureus 489	0.25	50.06	0.25	0.5	≤0.06	4	≤0.06	0.25	0.25	≤0.06	
Staphylococcus aureus 447	1	0.25	1	2	4	16	1	2	0.125	1	4
Staphylococcus aureus X400	0.25	≤0.06	0.25	1	0.125	8	0.25	0.5	4	≤0.06	≤0.06
Staphylococcus aureus X778	0.125	0.25	0.5	1	50.06	8	0.125	50.06	0.25	2	0.5
Staphylococcus aureus 491	0.5	0.25	0.5	0.5	0.5	8	0	1	50.06	0.125	0.5
Staphylococcus aureus S13E	50.06	50.06	0.25	2	0.125	8	0.125	0.5	1	1	0.25
Staphylococcus aureus SA1199	0.125	≤0.06	0.25	1	0.125	8	0.25	50.06	0.5	2	0.25
Staphylococcus aureus SA1199A	50.06	50.06	≤0.06	50.06	2	50.06	50.06	0.25	50.06	0.06	50.06
Staphylococcus aureus SA1199B	2	50.06	2	0.25	8	50.06	50.06	50.06	0.5	1	
Staphylococcus haemolyticus 105	4	2	1	1	8	64	2	2	1	1	4
Staphylococcus haemolyticus 415	8	8	4	1	32	>64	8	4	8	2	16
Staphylococcus epidermidis 270	1	0.25	1	0.25	1	16	1	2	16	0.5	1
Enterococcus faecium 180	2	1	0.5	0.5	4	8	4	8	2	0.25	1
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	4	≤0.06	≤0.06	2	≤0.06	≤0.06
Enterococcus faecalis 2041	≤0.06	≤0.06	≤0.06	0.06	0.125	8	0.25	0.5	50.06	50.06	
Enterococcus faecalis 276	1	0.5	0.5	1	0.25	8	0.125	1	0.125	50.06	50.06
Enterococcus gallinarum 245	8	8	4	1	32	4	0.25	0.5	0.125	2	16
Haemophilus influenzae RD											
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	50.06	50.06	50.06	50.06	50.06	50.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	150	151	152	153	154	155	156	157	158	159	160
Staphylococcus aureus 446	1	2	0.5	2	2	0.5	2	0.5	2	0.5	2
Staphylococcus aureus 489	0.5	\$0.06	0.5	1	0.5	1	0.5	2	0.25	0.25	0.21
Staphylococcus aureus 447	0.5	1	8	0.5	2	8	1	0.25	4	4	1
Staphylococcus aureus X400	\$0.06	\$0.06	1	0.5	2	1	2	0.5	4	4	4
Staphylococcus aureus X778	2	1	0.5	0.5	0.5	\$0.06	1	0.25	4	2	4
Staphylococcus aureus 491	\$0.06	0.5	1	0.125	0.5	1	1	\$0.06	1	2	0.125
Staphylococcus aureus S13E	0.25	0.25	0.5	0.125	0.25	1	1	0.25	2	1	1
Staphylococcus aureus SAI199	1	0.125	1	0.5	2	1	1	1	4	0.125	0.25
Staphylococcus aureus SAI199A	\$0.06	\$0.06	0.25	\$0.06	0.125	\$0.06	\$0.06	1	\$0.06	\$0.06	0.125
Staphylococcus aureus SAI199B	0.5	0.25	0.5	0.25	0.25	1	0.5	1	4	\$0.06	\$0.06
Staphylococcus haemolyticus 105	1	1	16	2	4	16	4	1	4	16	8
Staphylococcus haemolyticus 415	2	4	16	1	4	16	2	1	8	8	8
Staphylococcus epidermidis 270	0.25	0.5	4	0.25	0.5	1	1	0.25	4	0.5	1
Enterococcus faecium 180	0.25	0.25	4	0.125	1	4	1	\$0.06	0.25	2	0.5
Enterococcus faecium 180-1	\$0.06	\$0.06	0.125	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	\$0.06	\$0.06	0.125	\$0.06	0.125	0.125	0.5	\$0.06	1	0.125	\$0.06
Enterococcus faecalis 276	1	\$0.06	0.25	0.5	0.5	0.25	2	\$0.06	2	0.125	2
Enterococcus gallinarum 245	2	4	16	1	4	16	2	1	8	8	8
Haemophilus influenzae RD						16	2				
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	161	162	163	164	165	166	167	168	169	170	171
Staphylococcus aureus 446	0.5	0.5	1	2	1	2	1	≤0.06	0.25	2	1
Staphylococcus aureus 489	\$0.06	0.25	8	2	2	2	16	0.125	\$0.06	0.25	0.5
Staphylococcus aureus 447	1	50.06	0.5	2	0.5	2	4	50.06	2	0.5	1
Staphylococcus aureus X400	0.5	50.06	0.5	0.5	0.5	1	1	≤0.06	0.5	0.5	\$0.06
Staphylococcus aureus X778	0.5	50.06	2	1	0.125	1	16	0.5	≤0.06	1	≤0.06
Staphylococcus aureus 491	0.5	0.25	≤0.06	1	0.5	0.5	2	0.5	0.25	0.5	0.25
Staphylococcus aureus S13E	0.125	50.06	1	4	50.06	4	4	≤0.06	≤0.06	0.25	≤0.06
Staphylococcus aureus SA1199	0.25	50.06	2	2	0.25	2	2	0.5	≤0.06	1	0.25
Staphylococcus aureus SA1199A	\$0.06	50.06	0.5	0	≤0.06	0.125	4	≤0.06	≤0.06	≤0.06	≤0.06
Staphylococcus aureus SA1199B	0.25	50.06	1	2	1	2	4	1	0.125	0.25	0.25
Staphylococcus haemolyticus 105	4	0.25	8	2	4	2	32	0.5	2	4	4
Staphylococcus haemolyticus 415	8	2	8	2	4	2	16	2	4	4	8
Staphylococcus epidermidis 270	1	≤0.06	4	1	1	0.5	8	0.125	0.25	1	1
Enterococcus faecium 180	2	50.06	1	0.5	0.5	0.25	2	0.25	1	2	1
Enterococcus faecium 180-1	\$0.06	50.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	\$0.06	50.06	1	1	≤0.06	≤0.06	8	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 276	0.125	50.06	1	1	0.5	0.5	4	0.125	50.06	0.5	0.125
Enterococcus gallinarum 245	8	2	8	2	4	2	16	2	4	4	8
Haemophilus influenzae RD										>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	\$0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

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**TABLE 3**  
**In Vitro Activity of Formula I Compounds**  
**MIC (mcg/ml)/Compound**

Organism	172	173	174	175	176	177	178	179	180	181	182
Staphylococcus aureus 446	4	4	0.5	1	2	0.5	1	0.125	0.125	50.06	2
Staphylococcus aureus 489	0.5	2	≤0.06	0.25	0.5	≤0.06	0.125	≤0.06	50.06	50.06	2
Staphylococcus aureus 447	0.5	4	4	1	1	4	0.5	0.25	0.125	50.06	0.25
Staphylococcus aureus X400	0.5	4	≤0.06	0.125	1	≤0.06	0.125	≤0.06	50.06	50.06	1
Staphylococcus aureus X778	2	4	≤0.06	0.5	1	2	1	≤0.06	50.06	50.06	2
Staphylococcus aureus 491	0.5	2	1	0.5	2	0.5	0.125	0.125	0.5	50.06	1
Staphylococcus aureus S13E	≤0.06	4	≤0.06	0.25	2	0.25	0.5	0.25	50.06	50.06	0.25
Staphylococcus aureus SA1199	1	2	≤0.06	≤0.06	2	0.25	1	1	0.125	50.06	2
Staphylococcus aureus SA1199A	≤0.06	0.5	≤0.06	0.5	>64	0.5	≤0.06	≤0.06	50.06	50.06	50.06
Staphylococcus aureus SA1199B	≤0.06	4	0.125	≤0.06	1	0.25	1	0.125	50.06	50.06	4
Staphylococcus haemolyticus 105	0.25	2	4	2	4	4	1	0.5	2	0.25	2
Staphylococcus haemolyticus 415	2	4	16	4	2	16	2	1	2	1	4
Staphylococcus epidermidis 270	0.5	2	2	0.5	0.5	1	0.25	0.25	0.125	0.125	0.25
Enterococcus faecium 180	0.5	0.5	2	1	2	4	0.25	0.25	8	4	2
Enterococcus faecium 180-1	≤0.06	0.5	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	≤0.06	0.5	≤0.06	≤0.06	0.125	0.25	≤0.06	≤0.06	0.25	0.125	1
Enterococcus faecalis 276	0.125	2	≤0.06	≤0.06	2	0.25	0.5	≤0.06	2	2	1
Enterococcus gallinarum 245	2	4	16	4	—	2	16	2	1	0.25	50.06
Haemophilus influenzae RD	32	>64	>64	16	8	>64	4	4	32	>64	
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	0.5	0.25	16	50.06	50.06	50.06	50.06	
streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	0.5	0.25	8	≤0.06	≤0.06	≤0.06	≤0.06	

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml)/Compound

Organism	183	184	185	186	189	190	191	192	193	194	195
Staphylococcus aureus 446	\$0.06	2	\$0.06	\$0.06	0.5	0.25	2	0.5	0.5	\$0.06	0.5
Staphylococcus aureus 489	\$0.06	\$0.06	\$0.06	\$0.06	1	0.125	2	1	0.125	0.125	1
Staphylococcus aureus 447	\$0.06	\$0.06	\$0.06	\$0.06	0.5	1	2	2	\$0.06	0.5	1
Staphylococcus aureus X400	\$0.06	0.5	\$0.06	\$0.06	0.125	\$0.06	1	1	0.25	\$0.06	2
Staphylococcus aureus X778	\$0.06	0.5	\$0.06	\$0.06	0.25	0.125	2	1	\$0.06	0.5	0.5
Staphylococcus aureus 491	0.125	0.5	\$0.06	\$0.06	\$0.06	0.125	1	0.5	\$0.06	\$0.06	0.5
Staphylococcus aureus S13E	\$0.06	1	\$0.06	\$0.06	0.5	0.125	2	1	\$0.06	\$0.06	2
Staphylococcus aureus SA1199	\$0.06	0.125	\$0.06	\$0.06	0.5	0.25	2	2	0.125	0.5	0.5
Staphylococcus aureus SA1199A	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.5	0.25	\$0.06	\$0.06	\$0.06	\$0.06
Staphylococcus aureus SA1199B	\$0.06	1	\$0.06	\$0.06	1	0.5	2	0.5	0.125	0.125	1
Staphylococcus haemolyticus 105	\$0.06	0.25	\$0.06	0.5	1	8	2	1	0.5	1	1
Staphylococcus haemolyticus 415	\$0.06	\$0.06	1	1	1	8	8	2	1	2	4
Staphylococcus epidermidis 270	\$0.06	4	\$0.06	0.125	0.25	2	2	1	0.25	0.5	0.25
Enterococcus faecium 180	2	8	0.125	2	0.125	8	4	0.25	\$0.06	\$0.06	0.5
Enterococcus faecium 180-1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.25	0.125	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 2041	\$0.06	1	\$0.06	\$0.06	\$0.06	\$0.06	1	0.125	\$0.06	\$0.06	\$0.06
Enterococcus faecalis 276	0.125	0.5	\$0.06	\$0.06	0.25	0.125	4	0.5	\$0.06	0.125	0.25
Enterococcus gallinarum 245	0.5	4	\$0.06	2	1	8	8	2	1	2	4
Haemophilus influenzae RD	>64	64	8		32	>64	>64	>64	>64	>64	32
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06		\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06		\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

Organism	196	197	198	199	200	201	202	203	204	205
Staphylococcus aureus 446	0.5	1	1	0.5	1	4	4	0.5	0.125	2
Staphylococcus aureus 489	1	2	0.125	2	0.25	8	4	0.5	0.25	0.5
Staphylococcus aureus 447	0.5	2	0.125	1	0.5	16	8	1	50.06	0.5
Staphylococcus aureus X400	0.5	2	0.5	2	1	4	4	1	0.125	0.5
Staphylococcus aureus X778	1	2	0.125	1	0.5	4	4	1	0.5	0.5
Staphylococcus aureus 491	0.25	1	\$0.06	0.5	0.125	4	8	1	50.06	0.5
Staphylococcus aureus S13E	1	2	0.125	0.5	0.5	8	4	2	0.5	0.5
Staphylococcus aureus SA1199	0.5	2	0.5	1	1	8	8	2	0.125	1
Staphylococcus aureus SA1199A	\$0.06	1	\$0.06	0.125	\$0.06	2	2	0.5		\$0.06
Staphylococcus aureus SA1199B	0.5	2	0.5	1	1	16	8	1	0.25	0.5
Staphylococcus haemolyticus 105	0.5	1	0.5	2	1	8	4	1	0.5	1
Staphylococcus haemolyticus 415	1	4	1	4	2	8	8	2	0.25	1
Staphylococcus epidermidis 270	0.25	0.5	0.25	0.5	0.25	4	4	0.5	50.06	0.125
Enterococcus faecium 180	0.5	0.5	\$0.06	0.5	0.25	0.5	0.5	0.125	0.25	0.5
Enterococcus faecium 180-1	\$0.06	0.25	\$0.06	\$0.06	\$0.06	0.5	0.5	\$0.06	0.125	\$0.06
Enterococcus faecalis 2041	\$0.06	0.25	\$0.06	\$0.06	\$0.06	1	1	0.25	\$0.06	0.25
Enterococcus faecalis 276	0.25	1	0.25	1	0.5	4	4	0.5	\$0.06	0.5
Enterococcus gallinarum 245	1	4	1	4	2	8	8	2	0.25	1
Haemophilus influenzae RD	32	32	32	32	32	32	32	16	2	16
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06

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**TABLE 3**  
**In Vitro Activity of Formula I Compounds**  
**MIC (mcg/ml)/Compound**

Organism	206	207	208	209	210	211	212	213	214	215
Staphylococcus aureus 446	0.5	8	1	1	2	1	≤0.06	≤0.06	1	0.5
Staphylococcus aureus 489	1	4	0.5	1	1	0.25	≤0.06	≤0.06	1	2
Staphylococcus aureus 447	0.5	8	1	1	0.5	0.5	0.25	0.25	2	0.5
Staphylococcus aureus X400	0.5	8	0.25	1	≤0.06	0.5	≤0.06	≤0.06	0.5	0.5
Staphylococcus aureus X778	0.5	8	0.125	1	1	≤0.06	≤0.06	≤0.06	1	≤0.06
Staphylococcus aureus 491	≤0.06	1	0.5	0.25	≤0.06	0.25	≤0.06	≤0.06	1	0.25
Staphylococcus aureus S13E	1	8	0.25	0.5	≤0.06	0.5	≤0.06	≤0.06	1	2
Staphylococcus aureus SA1199	0.5	8	0.5	0.25	0.5	0.5	≤0.06	≤0.06	0.5	≤0.06
Staphylococcus aureus SA1199A	≤0.06	4	≤0.06	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.5	0.5
Staphylococcus aureus SA1199B	1	16	0.5	0.5	0.125	1	≤0.06	≤0.06	1	1
Staphylococcus haemolyticus 105	0.5	8	0.25	0.5	1	0.5	1	0.5	1	2
Staphylococcus haemolyticus 415	1	1	2	1	1	0.5	1	2	2	1
Staphylococcus epidermidis 270	0.25	8	0.5	0.125	0.25	0.5	≤0.06	0.5	≤0.06	0.125
Enterococcus faecium 180	≤0.06	1	0.25	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.25	≤0.06
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	0.25	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125	0.25
Enterococcus faecalis 276	≤0.06	0.25	0.125	0.25	≤0.06	≤0.06	≤0.06	≤0.06	0.25	2
Enterococcus gallinarum 245	1	1	2	1	1	≤0.06	1	2	2	64
Haemophilus influenzae RD		32	16	>64	>64	>64	32	32	>64	
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	
Streptococcus pyogenes C203		≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	

TABLE 3  
In vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

Organism	216	217	218	219	220	221	222	223	224	225
Staphylococcus aureus 446	1	0.25	4	8	1	1		0.25	0.5	1
Staphylococcus aureus 489	1	≤0.06	1	8	0.5	0.25	0.125	1	0.25	2
Staphylococcus aureus 447	1	1	1	8	0.5	0.5	0.5	0.5	0.5	1
Staphylococcus aureus X400	1	≤0.06	0.25	8	0.5	0.5	0.125	1	0.125	1
Staphylococcus aureus X778	0.25	≤0.06	1	8	0.5	0.5	≤0.06	1	0.125	0.5
Staphylococcus aureus 491	1	0.25	0.5	4	≤0.06	0.125	0.125	0.125	0.125	1
Staphylococcus aureus S13E	1	≤0.06	32	8	0.5	0.5	≤0.06	0.5	0.25	1
Staphylococcus aureus SA1199	≤0.06	≤0.06	4	4	1	1	1	2	0.25	1
Staphylococcus aureus SA1199A	1	≤0.06	≤0.06	1	≤0.06	≤0.06	0.125	≤0.06	≤0.06	0.25
Staphylococcus aureus SA1199B	0.5	0.125	0.25	8	0.5	1	0.125	1	0.5	2
Staphylococcus haemolyticus 105	0.5	2	0.5	2	0.5	1	1	1	1	0.5
Staphylococcus haemolyticus 415	0.25	8	4	2	0.5	2	1	1	0.5	4
Staphylococcus epidermidis 270	0.125	0.5	1	4	1	0.125	0.5	0.5	0.25	1
Enterococcus faecium 180	≤0.06	2	≤0.06	1	0.125	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecium 180-1	≤0.06	≤0.06	≤0.06	1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Enterococcus faecalis 2041	0.25	≤0.06	0.25	2	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	0.125
Enterococcus faecalis 276	0.5	≤0.06	≤0.06	2	0.125	≤0.06	≤0.06	0.125	≤0.06	0.25
Enterococcus gallinarum 245	64	8	≤0.06	2	0.5	2	1	1	0.5	4
Haemophilus influenzae RD	>64	>64	32	>64	32	>64	>64	32	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06
Streptococcus pneumoniae P1	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06	≤0.06

TABLE 3  
In Vitro Activity of Formula I Compounds  
MIC (mcg/ml) /Compound

Organism	226	227	228	229	230	231	232	233	234	235
Staphylococcus aureus 446	1	2	4	1	0.25	0.25	4	4	4	0.5
Staphylococcus aureus 489	0.5	2	2	1	0.25	\$0.06	8	4	4	0.5
Staphylococcus aureus 447	0.5	2	4	2	0.5	0.25	16	16	8	0.25
Staphylococcus aureus X400	0.25	1	1	1	0.5	\$0.06	8	8	8	0.125
Staphylococcus aureus X778	0.25	4	4	1	0.25	\$0.06	8	8	4	0.5
Staphylococcus aureus 491	0.25	2	1	0.5	0.125	\$0.06	4	8	8	0.125
Staphylococcus aureus S13E	0.5	4	8	1	0.5	\$0.06	8	8	8	0.125
Staphylococcus aureus SA1199	1	4	4	1	0.25	\$0.06	16	32	8	0.25
Staphylococcus aureus SA1199A	0.125	0.6	\$0.06	\$0.06	\$0.06	\$0.06	2	4	2	\$0.06
Staphylococcus aureus SA1199B	1	4	4	1	0.25	\$0.06	32	16	8	0.5
Staphylococcus haemolyticus 105	2	2	2	1	1	\$0.06	2	>64	8	0.5
Staphylococcus haemolyticus 415	1	4	4	2	2	0.5	32	>64	16	1
Staphylococcus epidermidis 270	1	2	2	0.5	0.5	0.125	8	8	4	0.5
Enterococcus faecium 180	\$0.06	0.25	1	\$0.06	\$0.06	\$0.06	0.5	2	1	0.5
Enterococcus faecium 180-1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	1	2	1	\$0.06
Enterococcus faecalis 2041	\$0.06	0.25	0.25	\$0.06	\$0.06	\$0.06	2	-	0.5	\$0.06
Enterococcus faecalis 276	0.25	0.5	1	0.25	\$0.06	\$0.06	8	8	4	0.125
Enterococcus gallinarum 245	1	4	4	2	2	0.5	32	>64	16	1
Haemophilus influenzae RD	32	>64	>64	2	32	32	16	>64	8	-
Escherichia coli EC14	>64	>64	>64	>64	>64	>64	>64	>64	>64	-
Streptococcus pyogenes C203	\$0.06	\$0.06	0.125	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	-
Streptococcus pneumoniae P1	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	\$0.06	0.5	0.25	\$0.06

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**TABLE 3**  
**In Vitro Activity of Formula I Compounds**  
**MIC (mcg/ml) /Compound**

Organism	236	237	238	239	240	241
Staphylococcus aureus 446	1	2	1	1	1	0.5
Staphylococcus aureus 489	4	0.5	0.5	0.5	1	0.5
Staphylococcus aureus 447	4	1	0.5	0.5	0.5	1
Staphylococcus aureus X400	2	1	1	0.25	0.25	0.5
Staphylococcus aureus X778	2	0.5	0.5	0.25	0.5	1
Staphylococcus aureus 491	4	0.25	0.25	0.25	0.25	0.25
Staphylococcus aureus S13E	4	0.25	0.125	0.5	0.5	0.25
Staphylococcus aureus SA1199	4	1	0.5	0.5	0.5	1
Staphylococcus aureus SA1199A	2	0.06	0.06	0.06	0.06	0.06
Staphylococcus aureus SA1199B	4	0.25	0.5	0.5	0.25	1
Staphylococcus haemolyticus 105	4	1	0.5	1	1	1
Staphylococcus haemolyticus 415	4	1	2	1	2	1
Staphylococcus epidermidis 270	2	0.5	0.5	0.25	0.25	0.5
Enterococcus faecium 180	1	0.25	0.125	0.06	0.06	0.06
Enterococcus faecium 180-1	1	0.06	0.06	0.06	0.06	0.06
Enterococcus faecalis 2041	1	0.125	0.06	0.06	0.06	0.06
Enterococcus faecalis 276	2	1	0.06	0.25	0.5	0.06
Enterococcus gallinarum 245	4	1	0.06	1	2	0.06
Haemophilus influenzae RD	3.2	8	>64	>64	>64	>64
Escherichia coli EC14	>64	>64	>64	>64	>64	>64
Streptococcus pyogenes C203	50.06	50.06	50.06	50.06	50.06	50.06
Streptococcus pneumoniae P1	50.06	50.06	50.06	50.06	50.06	50.06

The formula I compounds have also shown *in vivo* antimicrobial activity against experimentally-induced infections in laboratory animals. When two doses of test compound were administered to mice experimentally infected with the test organism, the activity observed was measured as an ED<sub>50</sub> value (effective dose in mg/kg to protect 50% of the test animals: see W. Wick et al., *J. Bacteriol.* 81, 233-235 (1961)). ED<sub>50</sub> values observed for illustrative compounds are given in Table 4.

TABLE 4

In Vivo Activity of Formula I Compounds ED50 (mg/kg/2)				
	Staphylococcus aureus	Streptococcus pyogenes	Streptococcus pneumoniae	
5	vancomycin	1.2	0.8	1.1
10	A82846A	0.19	0.084	0.39
	A82846B	0.25	0.12	0.18
	A82846C	1.3	1.5	4.6
	1	0.086	0.052	0.025
	2	0.27	0.014	0.025
15	4	0.36	0.012	0.036
	5	0.13	0.039	0.036
	6	0.15	0.013	0.021
	8	0.12	>0.5	0.273
20	12	0.13	>0.5	>0.5
	14	0.43	0.37	>0.5
	22	0.049	>0.5	>.05
	25	0.16	0.087	0.088
	29	0.088	0.1	0.054
25	32	0.055	0.034	0.039
	36	0.19	0.28	0.31
	39	0.1	0.045	<0.031
	41	n.d.	0.082	0.087
	46	n.d.	0.378	0.156
30	49	0.053	0.045	<0.031
	50	0.1	0.047	0.057
	51	0.16	0.057	0.036
	52	0.052	0.046	0.074
	53	0.077	0.16	0.071
35	57	0.041	0.054	0.046
	64	n.d.	0.044	<0.031
	87	n.d.	0.054	0.027
	90	n.d.	0.058	0.049
40	93	n.d.	0.074	0.012
	94	n.d.	0.16	0.049
	97	n.d.	0.066	0.038
	100	n.d.	0.062	0.046
	104	n.d.	0.12	0.041
45	105	n.d.	0.12	0.041
	106	n.d.	0.2	0.036
	107	n.d.	0.27	0.092
	108	n.d.	0.046	0.041
	111	n.d.	0.099	0.084
50	114	n.d.	0.091	0.76
	116	n.d.	0.89	0.058
	118	n.d.	0.91	0.046
	119	n.d.	0.16	0.08
	120	n.d.	0.058	0.005
55	121	n.d.	0.041	0.047

TABLE 4

In Vivo Activity of Formula I Compounds ED50 (mg/kg/2)			
Compound	Staphylococcus aureus	Streptococcus pyogenes	Streptococcus pneumoniae
122	n.d.	0.23	0.31
123	n.d.	0.076	0.039
124	n.d.	0.092	0.041
131	n.d.	<0.031	0.077
204	n.d.	<0.031	0.046
211	n.d.	<0.031	0.041
223	n.d.	<0.031	<0.031
229	n.d.	0.058	0.078
230	n.d.	0.046	0.078
n.d. = not done			

One important aspect of the antimicrobial activity of many of the formula I compounds is their activity against vancomycin-resistant enterococci. This activity is illustrated in Table 5, which summarizes a comparison of the activity of illustrative compounds against representative vancomycin-resistant and vancomycin-susceptible enterococci (*Enterococcus faecium* and *Enterococcus faecalis*, mean geometric MIC (mcg/mL)), as determined using the standard broth micro-dilution assay. End points were read after 24-hour incubation. Modification of the amino sugar of the disaccharide moiety provides improved activity against vancomycin-resistant strains over the parent glycopeptide antibiotic.

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TABLE 5

	Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
5	vancomycin	282	3.9
10	A82846A	>64	1.7
	A82846B	29	0.22
	A82846C	353	1.3
15	1	0.25	0.0061
	2	0.044	0.00038
	3	2.8	0.11
	4	0.50	0.062
	5	0.50	0.072
	6	1.2	0.14
20	7	2.8	0.43
	8	1.0	0.57
	9	11	0.38
	10	3.4	3.5
	11	6.7	0.22
25	12	1.7	1.1
	13	19	0.76
	14	0.50	0.76
	15	6.7	0.14
30	16	9.5	0.67
	17	9.5	0.38
	18	6.7	0.38
	19	4.8	0.22
	20	4.8	0.38
	21	5.7	4.3
35	22	1.0	1.5
	23	5.7	2.0
	24	54	0.67
	25	4.0	0.22
40	26	54	0.66
	27	45	1.5
	28	4.7	0.71
	29	0.21	0.031
	30	4.7	0.071
45	31	9.5	1.2
	32	0.50	0.089
	33	2.8	0.18
	34	4.0	3.4
	35	5.6	0.25
50	36	0.25	0.21
	37	2.4	0.25
	38	4.0	0.42
	39	1.2	0.09
	40	0.50	0.31
55	41	0.84	0.21

TABLE 5

	Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
5	42	1.7	0.089
10	43	13	1.1
	44	13	0.50
	45	2.0	0.50
	46	0.71	0.50
15	47	4.7	0.57
	48	4.8	0.50
	49	0.71	0.083
	50	0.12	0.054
	51	0.84	0.22
20	52	0.59	0.11
	53	0.35	0.25
	54	1.7	0.56
	55	13	1.7
	56	19	1.0
25	57	0.35	0.041
	58	5.7	0.76
	59	51	0.42
	60	19	3.0
	61	16	0.65
30	62	9.5	0.22
	63	54	0.66
	64	0.71	0.077
	65	2.4	0.20
	66	16	0.76
35	67	1.7	0.16
	68	6.7	0.25
	69	13	0.44
	70	2.0	0.092
40	71	11	0.57
	72	4.7	0.28
	73	11	0.25
	74	11	0.33
	75	16	0.50
45	76	8.0	0.29
	78	16	0.76
	79	0.84	0.042
	80	1.7	0.25
	81	1.0	0.042
50	82	22	0.50
	83	54	1.7
	84	23	0.66
	85	3.4	0.11
	86	1.4	0.036
55	87	0.71	0.047

TABLE 5

	Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
5	88	1.7	0.055
10	89	11	0.44
	90	0.71	0.041
15	91	2.8	0.11
	92	1.7	0.082
	93	0.42	0.042
20	94	0.50	0.041
	95	1.7	0.054
	96	1.4	0.11
25	97	0.71	0.054
	98	2.4	0.095
30	99	72	0.76
	100	0.71	0.042
	101	4.0	0.25
	102	2.0	0.13
35	103	4.0	0.33
	104	1.2	0.062
	105	0.84	0.062
	106	0.71	0.034
40	107	0.59	0.082
	108	0.84	0.04
	109	72	0.22
	110	1.7	0.047
	111	0.71	0.031
45	112	1.4	0.072
	113	0.84	0.054
	114	0.59	0.031
	115	8.0	0.19
	116	0.42	0.031
50	117	4.8	0.14
	118	0.84	0.048
	119	0.59	0.048
	120	1.0	0.072
	121	1.0	0.063
55	122	1.0	0.054
	123	1.0	0.041
	124	0.84	0.047
	125	3.4	0.14
	126	2.4	0.11
	127	1.2	0.33
	128	2.0	0.11
	129	27	1.52
	130	4.8	0.22
	131	0.84	0.028
	132	1.2	0.048

TABLE 5

	Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
5	133	4.0	0.13
10	134	2.0	0.13
	135	4.8	0.22
15	136	23	0.76
	137	6.7	0.38
20	138	38	0.87
	139	23	0.38
25	140	6.7	0.19
	141	8.0	0.25
30	142	45	1.5
	143	2.0	0.048
35	144	11	9.2
	145	64	1.3
40	146	64	1.5
	147	25	1.3
45	148	0.15	0.052
	149	45	0.66
50	150	1.7	0.25
	151	4.5	0.14
55	152	27	1.2
	153	1.4	0.083
	154	2.8	0.072
	155	128	1.3
	156	5.7	0.17
	157	2.0	0.054
	158	1.7	1.0
	159	27	0.50
	160	9.5	0.22
	161	23	0.44
	162	4.8	0.12
	163	2.0	0.87
	164	1.7	0.11
	165	4.0	0.062
	166	1.7	0.055
	167	1.0	0.055
	168	3.4	0.10
	169	19	0.50
	170	8.0	0.22
	171	9.5	0.22
	172	3.4	0.13
	173	2.0	0.12
	174	19	0.76
	175	9.5	0.22
	176	1.2	0.13
	178	2.8	0.13

TABLE 5

	Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
5	179	1.7	0.060
10	180	>128	0.71
	181	8.0	0.060
	182	13	0.250
	183	23	0.130
15	184	27	0.570
	185	4.7	0.060
	186	11	0.290
	189	2.4	0.10
20	190	6.7	0.29
	191	6.7	0.57
	192	0.84	0.035
	193	2	0.072
	194	2.4	0.083
	195	2.0	0.042
25	196	1.7	0.027
	197	1.2	0.16
	198	3.4	0.062
	199	1.4	0.036
30	200	1.4	0.041
	201	1.2	0.44
	202	1.4	0.76
	203	1.0	0.036
	204	0.71	0.031
35	205	1	0.036
	206	1.7	0.095
	207	1.2	0.50
	208	2.8	0.17
	209	1.2	0.136
40	210	0.84	0.041
	211	0.35	0.024
	212	0.50	0.036
	213	1.0	0.55
	214	0.71	0.024
45	215	2.8	0.25
	216	0.35	0.032
	217	13	0.57
	218	1.0	0.11
50	219	0.71	0.044
	220	0.71	0.05
	221	0.71	0.041
	222	0.84	0.072
	223	0.79	0.055
55	224	0.63	0.055
	225	0.63	0.072

TABLE 5

Compound No.	Vancomycin Resistant Strains	Vancomycin Sensitive Strains
226	1.6	0.041
227	0.71	0.11
228	1.0	0.14
229	0.50	0.024
230	0.35	0.031
231	1.7	0.11
232	0.71	0.29
233	1.7	1.7
234	2	2
235	2.4	0.25
236	1.4	0.5
237	1.0	0.048
238	1.4	0.14
239	2.8	0.095
240	1.19	0.055
241	1.4	0.048

A number of the lactic acid bacteria including all Leuconostocs, all Pedicocci, and some Lactobacilli, are intrinsically resistant to vancomycin. With the increased use of vancomycin, infections due to these bacteria have been reported with increasing frequency in immunocompromised patients (Handwerger et al., Reviews of Infectious Disease 12:602-610 (1990); Ruoff et al., Journal of Clinical Microbiology 26:2064-2068 (1988)). One important aspect of the antimicrobial activity of the formula I compounds is their activity against the vancomycin-resistant lactic acid bacteria. The compounds of the present are useful in inhibiting the growth of vancomycin-resistant lactic acid bacteria such as Leuconostoc, Pedicocci, and Lactobacilli and thus, controlling opportunistic infections by this group of bacteria. This activity is illustrated in Table 6, which summarizes a comparison of the activity of illustrative compounds against representative vancomycin-resistant lactic acid bacteria (*Pedicoccus acidilacti*, *Pedicoccus pentosaceus*, *Leuconostoc lactis*, *Leuconostoc mesenteroides*, *Leuconostoc pseudomesenteroides*, *Leuconostoc citreum*, and *Lactobacillus confusus*, mean geometric MIC (mcg/mL)), as determined using a standard agar dilution assay on brain-heart infusion agar.

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**Table 6**  
**In Vitro Activity of Formula I Compounds**  
**MIC (mcg/ml) / Compound**

	Pediococcus acidilactici (mean of 10)	Pediococcus pentosaceus (mean of 2)	Leuconostoc lactis (mean of 2)	Leuconostoc mesenteroides (mean of 4)	Leuconostoc pseudomesenter- oides	Leuconostoc citreum	Lactobacillus confusus
Vancomycin	891	1024	1024	1024	>1024	>1024	1024
A82846B	141	>256	64	>256	>256	>256	>256
1	18	23	23	64	>128	>128	64
2	5.9	1.1	4.0	16	32	64	16
4	7.5	16	16	16	32	128	32
5	2.8	8.0	8.0	8	16	64	16
6	4.3	8.0	8.0	9.5	16	64	16
14	3.7	5.7	8.0	11	32	64	32
29	4.0	8.0	5.7	6.7	16	32	8
32	12.1	16	16	16	32	64	16
36	9.2	16	16	16	32	32	32
39	26	32	32	32	64	>64	32
41	71	91	91	91	>128	>128	64
49	55	64	64	64	128	128	64
50	51	64	64	64	128	128	64
51	87	91	64	76	>128	>128	64
52	55	64	64	76	64	>128	64
58	55	64	64	64	128	128	64
108	12	23	8.0	10	32	64	16
118	16	16	11	13	32	64	16
122	24	16	16	16	32	64	16
124	20	16	16	16	64	64	16

Pharmaceutical formulations of the formula I compounds are also part of this invention. Thus, the compound, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral administration for the therapeutic or prophylactic treatment of bacterial infections.

For example, the compound can be admixed with conventional pharmaceutical carriers and excipients and used in the form of tablets, capsules, elixirs, suspensions, syrups, wafers, and the like. The compositions comprising a formula I compound will contain from about 0.1 to about 90% by weight of the active compound, and

more generally from about 10 to about 30%. The compositions may contain common carriers and excipients, such as corn starch or gelatin, lactose, sucrose, microcrystalline cellulose, kaolin, mannitol, dicalcium phosphate, sodium chloride, and alginic acid.

Disintegrators commonly used in the formulations of this invention include croscarmellose, microcrystalline cellulose, corn starch, sodium starch glycolate and alginic acid.

Tablet binders that can be included are acacia, methylcellulose, sodium carboxymethylcellulose, polyvinylpyrrolidone (Povidone), hydroxypropyl methylcellulose, sucrose, starch and ethylcellulose.

Lubricants that can be used include magnesium stearate or other metallic stearates, stearic acid, silicone fluid, talc, waxes, oils and colloidal silica.

Flavoring agents such as peppermint, oil of wintergreen, cherry flavoring or the like can also be used.

It may be desirable to add a coloring agent to make the dosage form more attractive in appearance or to help identify the product.

For intravenous (IV) use, a water soluble form of the antibiotic can be dissolved in one of the commonly used intravenous fluids and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution, or 5% dextrose solution can be used.

For intramuscular preparations, a sterile formulation of a suitable soluble salt form of the compound, for example the hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as pyrogen-free water (distilled), physiological saline or 5% glucose solution. A suitable insoluble form of the compound may be prepared and administered as a suspension in an aqueous base or a pharmaceutically acceptable oil base, for example, an ester of a long chain fatty acid such as ethyl oleate.

For oral use, a sterile formulation of a suitable salt form of the antibiotic, for example, the hydrochloride salt, formulated in a diluent such as distilled or deionized water, is particularly useful.

Alternatively, the unit dosage form of the antibiotic can be a solution of the antibiotic, preferably in its salt form, in a suitable diluent in sterile, hermetically sealed ampoules. The concentration of the antibiotic in the unit dosage may vary, for example, from about 1 percent to about 50 percent depending on the particular form of the antibiotic and its solubility and the dose desired by the physician.

In a further aspect, this invention provides a method for treating infectious diseases, especially those caused by Gram-positive microorganisms, in animals. The compounds of this invention are particularly useful in treating infections caused by methicillin-resistant staphylococci. Also, the compounds are useful in treating infection due to enterococci. Examples of such diseases are severe staphylococcal infections, for example, staphylococcal endocarditis and staphylococcal septicemia. The animal may be either susceptible to, or infected with, the microorganism. The method comprises administering to the animal an amount of a formula I compound which is effective for this purpose. In general, an effective amount of a formula I compound is a dose between about 0.5 and about 100 mg/kg. A preferred dose is from about 1 to about 60 mg/kg of active compound. A typical daily dose for an adult human is from about 50 mg to about 5 g.

In practicing this method, the antibiotic can be administered in a single daily dose or in multiple doses per day. The treatment regimen may require administration over extended periods of time, for example, for several days or for one to six weeks. The amount per administered dose or the total amount administered will depend on such factors as the nature and severity of the infection, the age and general health of the patient, the tolerance of the patient to the antibiotic and the microorganism or microorganisms involved in the infection.

A convenient method of practicing the treatment method is to administer the antibiotic via intravenous infusion. In this procedure a sterile formulation of a suitable soluble salt of the antibiotic is incorporated in a physiological fluid, such as 5% dextrose solution, and the resulting solution is infused slowly IV. Alternatively, the piggy-back method of IV infusion can also be used.

In order to illustrate more fully the operation of this invention, the following examples are provided, but are not to be construed as a limitation on the scope of the invention.

## EXAMPLE 1

### METHOD A

#### Preparation of Compound 2

A mixture of A82846B-triacetate, (2.25 g, 1.27 mmol, 1.0 equivalents (eq)) in 1:1 DMF/methanol (140 mL) under an atmosphere of argon was treated with 4-biphenylcarboxaldehyde (331 mg, 2.12 mmol, 1.7 eq). The resulting mixture was heated to 70°C and maintained as such for 1.75-2 hours. The solution was then treated with sodium cyanoborohydride (554 mg, 8.83 mmol, 6.9 eq). Heating at 70°C was continued for an additional 1.75-2 hours after which the reaction mixture was cooled to room temperature, concentrated *in vacuo*, diluted

with water (150 mL), and lyophilized to give a solid.

The solid was purified by preparative reverse-phase high performance liquid chromatography (HPLC) using a Waters 3 x (40 x 100 mm) C18 Nova-Pak cartridge with Waters C18 Nova-pak guard insert and utilizing a TEAP buffer system. The analytical method for analysis was: 0.2% TEA/phosphoric acid (TEAP), pH = 3, the gradient system at time 0 was 5% CH<sub>3</sub>CN/94.8% H<sub>2</sub>O with 0.2% TEAP held constant and at 20 minutes was 60% CH<sub>3</sub>ON/39.8% H<sub>2</sub>O with 0.2% TEAP held constant. The UV wavelength used was 235 nm and the flow rate was 2 ml/minute. Analysis was done using a Waters Nova-pak C18 RCM column (8 X 100mm) with a Nova-pak C18 guard insert. It is necessary to desalt the product after reverse phase purification when this HPLC method is used.

Desalting was accomplished by adding the purified product to 5-10 ml of H<sub>2</sub>O. 1 N HCl was added dropwise with stirring to dissolve the sample. The pH at this point was approximately 1-3. The pH of the solution was then raised to 8.2 with 1 N NaOH. A white solid precipitated out of solution. The mixture was cooled, filtered, and dried under vacuum at room temperature for 8-15 hours to give the zwitter ion (or neutral compound) of the desired product, compound 2 (*p*-phenylbenzyl-A82846B), (1.02 g, 45%).

## 15 EXAMPLE 2

### Preparation of Compound 4

20 A mixture of A82846B.triacetate (1.5 g, 0.848 mmol, 1.0 eq) in methanol (100 mL) under an atmosphere of argon was treated with *p*-phenoxybenzaldehyde (298 mg, 1.51 mmol, 1.8 eq). The resulting mixture was heated to reflux and maintained as such for 2 hours. The solution was then treated with sodium cyanoborohydride (326 mg, 5.18 mmol, 6.1 eq). Heating at reflux was continued for an additional 2 hours after which the reaction mixture was cooled to room temperature and evaporated to dryness *in vacuo*.

25 The product was purified by reverse-phase HPLC with a TFA buffer. The analytical method for analysis was accomplished by using a Waters Nova-pak C18 RCM column (8 x 100 mm) with a Nova-pak C18 guard insert, eluting with a 2.0 ml/minute linear gradient of 15% acetonitrile/0.1% TFA at time zero to 80% acetonitrile/0.1% TFA at 15 minutes. The fractions containing the products were detected by ultraviolet scan at 235 nm. The organic solvent of the desired fractions was removed and the mixture was lyophilized to a white solid 30 to give 0.618 mg of *p*-phenoxybenzyl-A82846B compound 4-tris(trifluoroacetate) salt (20% yield). No desalting or further purification was necessary. This method is also especially useful in the preparation of Compound 2 wherein phenylbenzaldehyde is one of the starting materials.

## 35 EXAMPLE 3

### Method B

### Preparation of Compound 176

40 A mixture of A82846B.triacetate (280 mg, 0.157 mmol, 1.0 eq) in 1:1 DMF/methanol (30 mL) was treated with 8-phenyloctanal (59 mg, 0.29 mmol, 1.8 eq) and sodium cyanoborohydride (60 mg, 0.95 mmol, 6.1 eq). The resulting mixture was heated, under an atmosphere of nitrogen, to 70°C and maintained as such for 1 hour. The reaction mixture was then cooled to room temperature and concentrated in *vacuo* to give a residue. Purification of the product was accomplished by reverse-phase preparative HPLC utilizing a Waters 2 x (40 x 100 mm) C18 Nova-Pak cartridge with Waters C18 Nova-Pak guard insert. Elution was accomplished with a 30 minute linear gradient (time=0 minutes 95% TEAP (0.5% aqueous triethylamine adjusted to pH=3 with phosphoric acid)/5% CH<sub>3</sub>CN to t = 30 minutes 20% TEAP/80% CH<sub>3</sub>CN) with a flow rate of 40 mL/minute and UV detection at 280 nm. The desired fraction was concentrated in *vacuo* then desalted with a Waters Sep-Pak cartridge as described below. This afforded compound 176 in 22% yield (60 mg).

45 The resulting compound was desalted as follows. A Waters Sep-Pak cartridge was pre-wet with methanol (2-3 column volumes) then conditioned with water (2-3 column volumes). The sample, dissolved in a minimum volume of water, was loaded onto the Sep-Pak column which was then washed with water (2-3 column volumes) to remove the unwanted salts. The product was then eluted with an appropriate solvent system, typically 1:1 CH<sub>3</sub>CN/H<sub>2</sub>O, CH<sub>3</sub>CN, and/or methanol. The organic solvent component was removed *in vacuo* and the resulting aqueous solution lyophilized to give the final product.

**EXAMPLE 4****Preparation of Compound 229**

5       A three liter 3-necked flask was fitted with a condenser, nitrogen inlet and overhead mechanical stirring apparatus. The flask was charged with pulverized A82846B acetate salt (20.0 g,  $1.21 \times 10^{-3}$  mol) and methanol (1000 mL) under a nitrogen atmosphere. 4'-chlorobiphenylcarboxaldehyde (2.88 g,  $1.33 \times 10^{-2}$  mol, 1.1 eq.) was added to this stirred mixture, followed by methanol (500 mL). Finally, sodium cyanoborohydride (0.84 g,  $1.33 \times 10^{-2}$  mol, 1.1 eq.) was added followed by methanol (500 mL). The resulting mixture was heated to reflux (about 65°C).

10      After 1 hour at reflux, the reaction mixture attained homogeneity. After 25 hours at reflux, the heat source was removed and the clear reaction mixture was measured with a pH meter (6.97 at 58.0°C). 1 N NaOH (22.8 mL) was added dropwise to adjust the pH to 9.0 (at 54.7°C). The flask was equipped with a distillation head and the mixture was concentrated under partial vacuum to a weight of 322.3 grams while maintaining the pot temperature between 40-45°C.

15      The distillation head was replaced with an addition funnel containing 500 mL of isopropanol (IPA). The IPA was added dropwise to the room temperature solution over 1 hour. After approximately 1/3 of the IPA was added, a granular precipitate formed. The remaining IPA was added at a faster rate after precipitation had commenced. The flask was weighed and found to hold 714.4 grams of the IPA/methanol slurry.

20      The flask was re-equipped with a still-head and distilled under partial vacuum to remove the remaining methanol. The resulting slurry (377.8 g) was allowed to chill in the freezer overnight. The crude product was filtered through a polypropylene pad and rinsed twice with 25 mL of cold IPA. After pulling dry on the funnel for 5 minutes, the material was placed in the vacuum oven to dry at 40°C. A light pink solid (22.87 g (theory = 22.43 g)) was recovered. HPLC analysis versus a standard indicated 68.0% weight percent of Compound 229 [4-[4-chlorophenyl]benzyl-A82846B] in the crude solid, which translated into a corrected crude yield of 69.3%.

25      The products of the reaction were analyzed by reverse-phase HPLC utilizing a Zorbax SB-C18 column with ultraviolet light (UV; 230 nm) detection. A 20 minute gradient solvent system consisting of 95% aqueous buffer/5% CH<sub>3</sub>CN at time=0 minutes to 40% aqueous buffer/60% CH<sub>3</sub>CN at time=20 minutes was used, where the aqueous buffer was TEAP (5 ml CH<sub>3</sub>CN, 3 ml phosphoric acid in 1000 ml water).

**EXAMPLE 5**

30      Table 7 summarizes the preparation and certain physical characteristics of the exemplified compounds. The yield of the product was calculated using the amount of the formula II compound as the limiting reagent. The following terms are found in Table 6 and are defined here. "Method" refers to the method of synthesis as described in Examples 1 and 2, or 3. "Reagent Equivalents" refers to the molar equivalents of the aldehyde and reducing agent relative to the formula II compound. "FAB-MS (M+3H)" refers to Fast atom bombardment-mass spectrometry.

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TABLE 7

	Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
5	1	28	A/1:1	1.7/6.9	1733*
10	2	45	A/1:1	1.7/6.9	1760
	3	28	A/1:1	1.8/7.6	1732**
	4	20	A/0:1	1.8/6.1	1776***
15	5	30	A/0:1	1.8/6.1	1790
	6	10	A/0:1	1.8/6.1	1768***
	7	55	A/0:1	1.8/6.1	1740***
	8	16	A/0:1	1.8/6.1	1826
20	9	32	A/0:1	1.8/6.1	1764***
	10	6	A/0:1	1.8/6.1	1868
	11	38	A/0:1	1.8/6.1	1784
	12	46	A/0:1	1.8/6.1	1940
	13	32	A/0:1	1.8/6.1	1783**
25	14	5.4	A/1:1	1.9/4.2	1859
	15	42	A/0:1	1.8/6.1	1763
	16	39	A/0:1	1.8/6.1	1807**
	17	41	A/0:1	1.8/6.1	1798
	18	27	A/0:1	1.8/6.1	1817
30	19	30	A/0:1	1.8/6.1	1739
	20	5	A/1:1	1.8/1.8	1775*
	21	11	A/1:1	1.8/1.8	1872*
	22	8	A/1:1	1.8/1.8	1829**
	23	ND	A/0:1	1.8/3.6	1888***
35	24	34	A/0:1	1.7/2.5	1685
	25	31	A/0:1	1.8/1.6	1779
	26	30	A/0:1	1.7/2.5	1685
	27	19	A/0:1	1.8/2.5	1734**
40	28	35	A/0:1	1.6/1.6	1735
	29	39	A/0:1	1.6/1.6	1785**
	30	29	A/0:1	1.6/1.6	1734**
	31	11	A/0:1	1.7/2.5	1684**
	32	28	A/0:1	1.5/1.6	1771**
45	33	ND	A/1:1	1.8/1.8	1789
	34	ND	A/1:1	1.8/1.8	1836
	35	ND	A/1:1	1.8/1.8	1785
	36	ND	A/1:1	1.8/1.8	1835
	37	31	A/0:1	1.5/1.5	1752***
50	38	16	A/0:1	1.5/1.6	1709
	39	46	A/0:1	1.5/1.5	1773
	40	29	A/1:1	1.8/1.8	1846*
	41	46	A/0:1	1.5/1.5	1729
	42	53	A/0:1	1.5/1.5	1780
55	43	22	A/0:1	1.1/1.5	1799***
	44	42	A/0:1	1.5/1.5	1749

TABLE 7

	Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
5	45	50	A/0:1	1.1/1.5	1841
10	46	38	A/0:1	1.1/1.5	1850
	47	40	A/0:1	1.5/1.5	1687
	48	22	A/0:1	1.5/1.5	1728***
	49	44	A/0:1	1.5/1.5	1776***
15	50	32	A/1:10	2.0/1.5	1774
	51	32	A/0:1	1.5/1.5	1820
	52	31	A/0:1	1.5/1.5	1819**
	53	43	A/0:1	1.5/1.5	1896
20	54	4	A/1:1	1.8/1.8	1789
	55	21	A/0:1	1.5/1.5	1767
	56	20	A/0:1	1.1/1.5	1741
	57	29	A/0:1	1.5/1.5	1820**
	58	22	A/0:1	1.5/1.5	1727
25	59	ND	A/1:1	1.8/1.8	1803
	60	33	A/0:1	1.1/1.5	1777**
	61	24	A/0:1	1.1/1.5	1723
	62	ND	A/1:1	1.8/1.8	1789**
30	63	ND	A/1:1	1.8/1.8	1789**
	64	30	A/0:1	1.5/1.5	1805
	65	24	A/0:1	1.1/1.5	1763
	66	17	A/0:1	1.1/1.5	1704***
	67	22	A/0:1	1.1/1.5	1766***
35	68	ND	A/1:1	1.8/1.8	1802
	69	ND	A/1:1	1.8/1.8	1803
	70	44	A/0:1	1.1/1.5	1821
	71	4	A/0:1	1.1/1.5	1796***
40	72	32	A/0:1	1.5/1.5	1750***
	73	ND	A/1:1	1.8/1.8	1753
	74	17	A/0:1	1.1/1.5	1815
	75	23	A/0:1	1.5/1.5	1806***
	76	16	A/1:1	1.8/1.8	1711
45	77	ND	A/1:1	1.8/1.8	1742
	78	5	A/1:1	1.8/1.8	1728
	79	ND	A/1:1	1.8/1.8	1783**
	80	46	A/0:1	1.5/1.5	1843****
	81	52	A/0:1	1.5/1.5	1844***
50	82	29	A/0:1	1.5/1.5	1726***
	83	7	A/0:1	1.5/1.5	1798**
	84	8	A/0:1	1.5/1.5	1700
	85	30	A/0:1	1.5/1.5	1775
	86	45	A/0:1	1.5/1.5	1809
55	87	42	A/0:1	1.1/1.5	1854**
	88	36	A/0:1	1.1/1.5	1854**

TABLE 7

	Compound No.	Yield (%)	Method/ DMP: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
5	89	43	A/1:1	1.8/1.8	1711
10	90	13	A/1:1	1.8/1.8	1787
15	91	20	A/1:10	1.5/1.5	1759**
20	92	23	A/1:10	1.5/1.5	1777
25	93	42	A/0:1	1.5/1.5	1823
30	94	41	A/0:1	1.1/1.5	1854**
35	95	49	A/0:1	1.1/1.5	1789**
40	96	34	A/0:1	1.1/1.5	1832
45	97	42	A/1:10	1.5/1.5	1773**
50	98	31	A/0:1	1/1.5	1805
55	99	ND	A/1:1	1.8/1.8	1770**
	100	ND	A/1:1	1.8/1.8	1787
	101	34	A/1:1	1.19/1.8	1761
	102	41	A/0:1	1.5/1.5	1805
	103	37	A/0:1	1/1.5	1788***
	104	34	A/0:1	1.1/1.5	1819**
	105	ND	A/1:1	1.7/2.0	1838*
	106	ND	A/1:1	1.7/2.0	1844
	107	ND	A/1:1	1.1/1.1	1802
	108	ND	A/0:1	1.8/1.8	1791**
	109	ND	A/0:1	1.8/1.8	1789
	110	15	A/0:1	1.1/1.5	1881
	111	ND	A/1:1	1.8/1.8	1843
	112	16	A/1:1	1.8/1.8	1764
	113	45	A/0:1	1.1/1.5	1805**
	114	52	A/0:1	1.1/1.5	1888**
	115	39	A/0:1	1.1/1.5	1791
	116	ND	A/1:1	1.8/2.0	1834
	117	29	A/0:1	1.5/1.7	1803**
	118	28	A/0:1	2/1.5	1765**
	119	41	A/0:1	1/1.5	1843
	120	38	A/0:1	1.1/1.5	1757
	121	41	A/0:1	1.1/1.5	1799
	122	24	A/1:1	1.8/2.6	1863
	123	55	A/0:1	1.1/1.5	1795**
	124	17	A/1:10	3/1.5	1781**
	125	36	A/0:1	1.5/1.8	1841
	126	26	A/0:1	1.6/1.8	1818
	127	54	A/0:1	1.1/1.5	1810
	128	34	A/0:1	1.4/1.8	1831
	129	ND	A/1:1	1.4/1.8	1780
	130	4	A/0:1	1.1/1.5	1795**
	131	42	A/0:1	1.1/1.5	1834**

TABLE 7

	Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
5	132	49	A/0:1	1.1/1.5	1843
10	133	41	A/0:1	1.1/1.5	1855
15	134	30	A/0:1	1.1/1.5	1801**
20	135	ND	A/1:1	1.8/1.8	1779
25	136	ND	A/1:1	1.8/1.8	1699
30	137	ND	A/1:1	1.8/1.8	1760
35	138	ND	A/1:1	1.8/1.8	1741
40	139	13	A/1:10	2.4/1.5	1749**
45	140	11	A/1:10	2.9/1.5	1750*
50	141	ND	A/1:1	2.3/5.3	1742
55	142	ND	A/1:1	2.5/5.4	1826
	143	ND	A/1:1	1.8/1.8	1861
	144	ND	A/1:1	1.5/1.5	1922
	145	ND	A/1:1	1.1/1.1	1716
	146	ND	A/1:1	1.35/1.8	1780*
	147	ND	A/1:1	1.5/1.8	1769
	148	31	A/1:10	3/1.5	1857
	149	18	A/0:1	1.1/1.5	1777
	150	22	A/1:1	2/4.8	1803
	151	ND	A/1:1	1.8/1.8	1760
	152	ND	A/1:1	1.8/1.8	1826****
	153	22	A/1:10	2.5/1.6	1782
	154	ND	A/1:1	1.8/1.8	1780
	155	13	A/0:1	1.6/1.6	1768
	156	41	A/1:9	1.2/1.6	1788
	157	9	A/1:1	2.7/5.4	1810
	158	ND	A/1:1	1.8/4.1	1854
	159	13	A/1:9	1/1.6	1807
	160	13	A/1:9	0.95/1.6	1774
	161	ND	A/1:1	1.8/1.8	1690
	162	ND	A/1:1	3.1/6.9	1804
	163	ND	A/1:1	1.9/5.3	1854
	164	ND	A/1:1	1.8/1.8	1772
	165	21	A/1:1	2.0/4.9	1810
	166	20	A/1:1	2.0/6.2	1870
	167	23	A/1:1	1.8/4.1	1914
	168	ND	A/1:1	1.8/1.8	1737
	169	15	A/1:1	1.8/4.1	1700
	170	39	A/0:1	1.2/1.1	1728
	171	32	A/0:1	1.2/1.5	1729**
	172	11	B/1:1	2.2/4.8	1755**
	173	51	A/1:9	1.3/1.7	1909
	174	35	A/1:9	1.5/1.6	1816

TABLE 7

	Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH3CN)	FAB-MS (M+3H)
5	175	22	B/1:1	1.9/6.2	1742
10	176	21	B/1:1	1.8/6.1	1782
15	177	ND	A/1:1	3.6/1.8	1774
20	178	33	A/1:9	1.4/1.7	1788**
25	179	22	B/1:1	1.8/3.8	1748
30	180	16	A/1:1	1.1/1.3	1591***
35	181	14	A/1:1	1.1/1.3	1617
40	182	17	A/0:1	1.6/6.3	1725
45	183	17	A/0:1	1.6/6.3	1691**
50	184	8	A/0:1	1.6/6.26	1707**
55	185	21	A/1:1	1.1/3.0	1725**
	186	8	A/1:1	1.1/3.0	1630**
	187	16	A/1:1	1.6/3.0	2110**
	188	6	A/1:1	1.5/5.0	2976**
	189	20	A/1:10	1/1.2	1747**
	190	9	A/1:10	1.5/1.5	1716
	191	18	B/1:1	1.8/4.1	1771**
	192	11	A/0:1	ND/1.8	1738
	193	24	A/1:10	2.0/1.5	1820**
	194	27	A/1:10	2.0/1.5	1821
	195	18	B/1:1	1.6/3.6	1798
	196	18	B/1:1	1.8/3.9	1754
	197	35	B/1:1	1.5/3.5	1810
	198	14	B/1:1	1.5/3.7	1784
	199	ND	B/1:1	1.5/2.8	1772
	200	11	B/1:1	1.5/3.7	1828
	201	14	B/1:1	1.8/6.3	1873**
	202	7	B/1:1	1.3/5.9	1889**
	203	15	A/0:1	1.1/1.1	1843
	204	16	B/1:1	2.0/5.6	1746
	205	23	B/1:1	1.8/3.7	1732
	206	11	A/0:1	1.1/1.1	1777
	207	11	B/1:1	1.6/4.2	1813**
	208	26	B/1:1	1.9/3.9	1703
	209	20	A/1:1	1.0/1.6	1774
	210	35	A/0:1	1.0/1.0	1788
	211	26	A/0:1	1.3/1.8	1777
	212	48	A/1:1	1.1/3.1	1849**
	213	56	A/1:1	1.0/3.6	1849**
	214	9	B/1:1	1.9/1.9	1732
	215	35	A/0:1	1.3/1.8	1820***
	216	31	A/0:1	1.3/1.8	1828***
	217	12	B/1:1	2.0/2.1	1676
	218	24	A/1:10	1.2/1.5	1766***

TABLE 7

Compound No.	Yield (%)	Method/ DMF: MeOH	Reagent Equivalents (aldehyde/ NaBH <sub>3</sub> CN)	FAB-MS (M+3H)
219	24	A/1:1	1.4/3.5	1860
220	21	A/0:1	1.3/1.8	1785
221	42	A/0:1	1.3/1.8	1787
222	20	A/0:1	1.1/1.1	1787
223	32	A/1:1	2.4/4.5	1817**
224	36	A/1:1	1.6/5.6	1773**
225	ND	A/0:1	1.1/1.1	1787
226	28	A/1:1	1.5/3.0	1766*
227	22	A/1:1	1.2/3.7	1777**
228	21	A/0:1	1/1.1	1848**
229	16	A/0:1	1/1.2	1793
230	27	A/0:1	1.3/1.8	1838***
231	36	A/0:1	1.3/1.8	1785*
232	32	A/1:1	1.8/4.6	1806
233	5	A/1:1	1.1/7.3	1878
234	7	B/1:1	1.5/3.5	1836*
235	15	B/1:1	1.4/4.8	1750
236	4	B/1:1	1.4/6.3	1819**
237	14	A/0:1	1.1/1.1	1787
238	25	B/0:1	1.1/1.1	1771
239	22	B/1:1	1.6/1.5	1810
240	4.7	A/1:60	1.2/1.1	1810***
241	24	B/1:1	1.1/2.5	1779**
242	N.D.	A/1:50	1.1/1.2	1787
243	20	A/0:1	1.1/1.1	1790
244	24	C/0:1	1.1/1.1	1808
N.D. = Not determined				
*M+H				
**M+2H				
***M+4H				
****M+6H				

**EXAMPLE 6**

45

Capsule Formulation

Capsules containing 250 mg of Compound 2 are prepared using the following ingredients:

Ingredient	Weight
Compound 2 HCl salt	255.4 mg
Corn starch flowable powder	150 mg
Corn starch	144.6 mg

Compound 2 (HCl salt form, 255.4 mg), corn starch flowable powder (150 mg) and corn starch (144.6 mg) are

blended in a suitable mixer until homogenous. The mixture is used to fill a hard gelatin capsule to a net fill weight of 550 mg.

#### **EXAMPLE 7**

5

##### Capsule Formulation

Capsules containing 250 mg of Compound 229 are prepared using the following ingredients:

	Ingredient	Weight
10	Compound 229 HCl salt	255.4 mg
15	Corn starch flowable powder	150 mg
	Corn starch	144.6 mg

Compound 2 (HCl salt form, 255.4 mg), corn starch flowable powder (150 mg) and corn starch (144.6 mg) are blended in a suitable mixer until homogenous. The mixture is used to fill a hard gelatin capsule to a net fill weight of 550 mg.

20

#### **EXAMPLE 8**

##### Suspension Formulation

25

A sterile insoluble form of compound 2 is milled or screened to a particle size suitable for suspension. This particulate material is suspended in the following vehicle:

	Ingredient	Weight
30	Lecithin	1%
	Sodium citrate	2%
	Propylparaben	0.015%
35	Distilled water	q.s. to desired volume

#### **EXAMPLE 9**

40

##### Suspension Formulation

A sterile insoluble form of compound 229 is milled or screened to a particle size suitable for suspension. This particulate material is suspended in the following vehicle:

	Ingredient	Weight
45	Lecithin	1%
	Sodium citrate	2%
	Propylparaben	0.015%
50	Distilled water	q.s. to desired volume

55

**EXAMPLE 10****Tablet Formulation**

5 Tablets containing 250 mg of compound 2 are prepared with the following composition:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

15

**EXAMPLE 11****Tablet Formulation**

20 Tablets containing 250 mg of compound 229 are prepared with the following composition:

Ingredient	Weight
Lecithin	1%
Sodium citrate	2%
Propylparaben	0.015%
Distilled water	q.s. to desired volume

30

**EXAMPLE 12****Tablet Formulation**

35 Tablets containing 250 mg of compound 2 are prepared with the following composition:

Ingredient	Weight
Compound 2 HCl salt	255.4 mg
Microcrystalline cellulose	101.1 mg
Croscarmellose sodium	12.0 mg
Providone	12.0 mg
Magnesium stearate	3.0 mg
Stearic acid	4.0 mg
Purified water	0.16 ml

50

**EXAMPLE 13****Tablet Formulation**

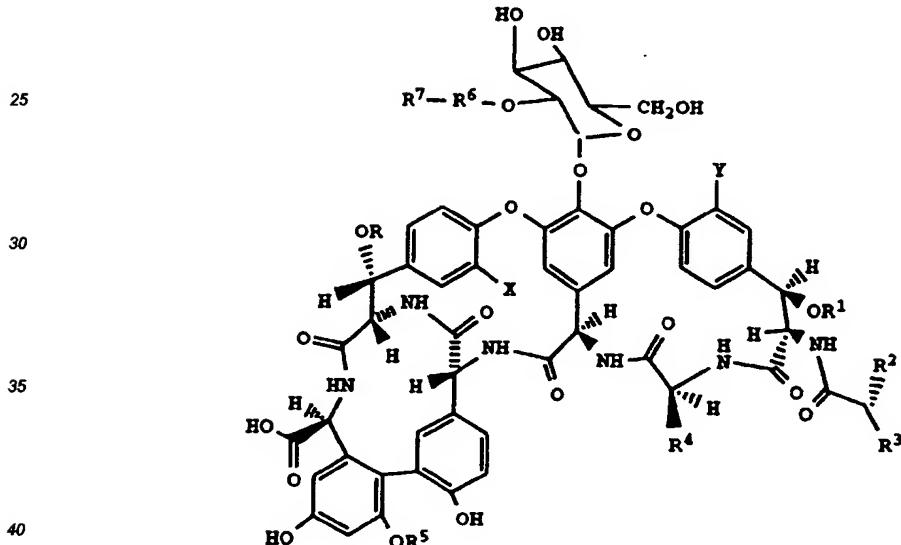
55 Tablets containing 250 mg of compound 229 are prepared with the following composition:

	Ingredient	Weight
5	Compound 229 HCl salt	255.4 mg
	Microcrystalline cellulose	101.1 mg
	Croscarmellose sodium	12.0 mg
10	Providone	12.0 mg
	Magnesium stearate	3.0 mg
	Stearic acid	4.0 mg
	Purified water	0.16 ml

15

**Claims**

20      1. A compound of the formula:



or salt thereof, wherein:

X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminy, actinosaminy, or ristosaminy;R<sup>1</sup> is hydrogen, or mannose;R<sup>2</sup> is -NH<sub>2</sub>, -NHCH<sub>3</sub>, or -N(CH<sub>3</sub>)<sub>2</sub>;R<sup>3</sup> is -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, [*p*-OH, *m*-Cl]phenyl, *p*-rhamnose-phenyl, [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, or [*p*-CH<sub>3</sub>O-rhamnose]phenyl;R<sup>4</sup> is -CH<sub>2</sub>(CO)NH<sub>2</sub>, benzyl, [*p*-OH]phenyl, or [*p*-OH, *m*-Cl]phenyl;R<sup>5</sup> is hydrogen, or mannose;R<sup>6</sup> is 4-*epi*-vancosaminy, L-acosaminy, L-ristosaminy, or L-actinosaminy;R<sup>7</sup> is (C<sub>2</sub>-C<sub>16</sub>)alkenyl, (C<sub>2</sub>-C<sub>12</sub>)alkynyl, (C<sub>1</sub>-C<sub>12</sub> alkyl)-R<sub>8</sub>, (C<sub>1</sub>-C<sub>12</sub> alkyl)-halo, (C<sub>2</sub>-C<sub>6</sub> alkenyl)-R<sub>8</sub>, (C<sub>2</sub>-C<sub>6</sub> alkynyl)-R<sub>8</sub>, (C<sub>1</sub>-C<sub>12</sub> alkyl)-O-R<sub>8</sub>, and is attached to the amino group of R<sup>6</sup>;R<sup>8</sup> is selected from the group consisting of:

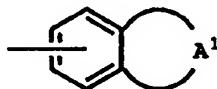
a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) hydroxy,

(ii) halo,  
 (iii) nitro,  
 (iv) ( $C_1$ - $C_6$ )alkyl,  
 (v) ( $C_1$ - $C_6$ )alkenyl,  
 (vi) ( $C_1$ - $C_6$ )alkynyl,  
 (vii) ( $C_1$ - $C_6$ )alkoxy,  
 (viii) halo-( $C_1$ - $C_6$ )alkyl,  
 (ix) halo-( $C_1$ - $C_6$ )alkoxy,  
 (x) carbo-( $C_1$ - $C_6$ )alkoxy,  
 (xi) carbobenzoyloxy,  
 (xii) carbobenzoyloxy substituted with ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, halo, or nitro,  
 (xiii) a group of the formula  $-S(O)_n-R^9$ , wherein n' is 0-2 and  $R^9$  is ( $C_1$ - $C_6$ )alkyl, phenyl, or phenyl substituted with ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, halo, or nitro, and  
 (xiv) a group of the formula  $-C(O)N(R^{10})_2$  wherein each  $R^{10}$  substituent is independently hydrogen, ( $C_1$ - $C_6$ )-alkyl, ( $C_1$ - $C_6$ )-alkoxy, phenyl, or phenyl substituted with ( $C_1$ - $C_6$ )-alkyl, ( $C_1$ - $C_6$ )-alkoxy, halo, or nitro;

b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:  
 (i) halo,  
 (ii) ( $C_1$ - $C_6$ )alkyl,  
 (iii) ( $C_1$ - $C_6$ )alkoxy,  
 (iv) halo-( $C_1$ - $C_6$ )alkyl,  
 (v) halo-( $C_1$ - $C_6$ )alkoxy,  
 (vi) phenyl,  
 (vii) thiophenyl,  
 (viii) phenyl substituted with halo, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkenyl, ( $C_1$ - $C_6$ )alkynyl, ( $C_1$ - $C_6$ )alkoxy, or nitro,  
 (ix) carbo-( $C_1$ - $C_6$ )alkoxy,  
 (x) carbobenzoyloxy,  
 (xi) carbobenzoyloxy substituted with ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, halo, or nitro,  
 (xii) a group of the formula  $-S(O)_n-R^9$ , as defined above,  
 (xiii) a group of the formula  $-C(O)N(R^{10})_2$  as defined above, and  
 (xiv) thienyl;

c) a group of the formula:



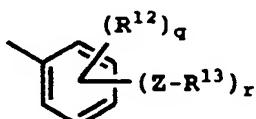
wherein  $A^1$  is  $-OC(A^2)_2-C(A^2)_2-O-$ ,  $-O-C(A^2)_2-O-$ ,  $-C(A^2)_2-O-$ , or  $-C(A^2)_2-C(A^2)_2-C(A^2)_2-C(A^2)_2-$ , and each  $A^2$  substituent is independently selected from hydrogen, ( $C_1$ - $C_6$ )-alkyl, ( $C_1$ - $C_6$ )-alkoxy, and ( $C_4$ - $C_{10}$ )-cycloalkyl;

d) a group of the formula:



wherein p is from 1 to 5; and  
 $R^{11}$  is independently selected from the group consisting of:  
 (i) hydrogen,  
 (ii) nitro,  
 (iii) hydroxy,  
 (iv) halo,  
 (v) ( $C_1$ - $C_6$ )-alkyl,

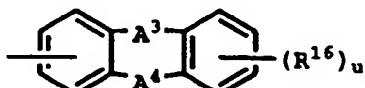
(vi)  $(C_1-C_8)$ alkoxy,  
 (vii)  $(C_8-C_{12})$ alkyl,  
 (viii)  $(C_2-C_9)$ alkynyl,  
 (ix)  $(C_9-C_{12})$ alkoxy,  
 5 (x)  $(C_1-C_3)$ alkoxy substituted with  $(C_1-C_3)$ alkoxy, hydroxy, halo $(C_1-C_3)$ alkoxy, or  $(C_1-C_4)$ alkylthio,  
 (xi)  $(C_2-C_6)$ alkenyoxy,  
 (xii)  $(C_1-C_{13})$ alkynyoxy  
 (xiii) halo- $(C_1-C_6)$ alkyl,  
 (xiv) halo- $(C_1-C_6)$ alkoxy,  
 10 (xv)  $(C_2-C_6)$ alkylthio,  
 (xvi)  $(C_2-C_{10})$ alkanoyloxy,  
 (xvii) carboxy- $(C_2-C_4)$ alkenyl,  
 (xviii)  $(C_1-C_3)$ alkylsulfonyloxy,  
 (xix) carboxy- $(C_1-C_3)$ alkyl,  
 15 (xx) N-[di( $C_1-C_3$ )-alkyl]amino- $(C_1-C_3)$ alkoxy,  
 (xxi) cyano- $(C_1-C_6)$ alkoxy, and  
 (xxii) diphenyl- $(C_1-C_6)$ alkyl,  
 with the proviso that when  $R^{11}$  is  $(C_1-C_8)$ alkyl,  $(C_1-C_8)$ alkoxy, or halo, p must be greater or equal to 2,  
 20 or when  $R^7$  is  $(C_1-C_3)$ alkyl- $R^8$  then  $R^{11}$  is not hydrogen,  $(C_1-C_8)$ alkyl,  $(C_1-C_8)$ alkoxy, or halo;  
 e) a group of the formula:



25 wherein q is 0 to 4;  
 R<sup>12</sup> is independently selected from the group consisting of:  
 30 (i) halo,  
 (ii) nitro,  
 (iii)  $(C_1-C_8)$ alkyl,  
 (iv)  $(C_1-C_8)$ alkoxy,  
 (v) halo- $(C_1-C_6)$ alkyl,  
 35 (vi) halo- $(C_1-C_6)$ alkoxy, and  
 (vii) hydroxy, and  
 (viii)  $(C_1-C_6)$ thioalkyl;  
 r is 1 to 5; provided that the sum of q and r is no greater than 5;  
 Z is selected from the group consisting of:  
 40 (i) a single bond,  
 (ii) divalent  $(C_1-C_6)$ alkyl unsubstituted or substituted with hydroxy,  $(C_1-C_6)$ alkyl, or  $(C_1-C_6)$ alkoxy,  
 (iii) divalent  $(C_2-C_6)$ alkenyl,  
 (iv) divalent  $(C_2-C_6)$ alkynyl, or  
 45 (v) a group of the formula  $-(C(R^{14})_2)s-R^{15}-$  or  $-R^{15}-(C(R^{14})_2)s-$ , wherein s is 0-6; wherein each  $R^{14}$  substituent is independently selected from hydrogen,  $(C_1-C_6)$ alkyl, or  $(C_4-C_{10})$ cycloalkyl; and  $R^{15}$  is selected from -O-, -S-, -SO-, -SO<sub>2</sub>-, -SO<sub>2</sub>O-, -C(O)-, -OC(O)-, -C(O)O-, -NH-, -N( $C_1-C_6$  alkyl)-, and -C(O)NH-, -NHC(O)-, N=N;  
 R<sup>13</sup> is independently selected from the group consisting of:  
 50 (i)  $(C_4-C_{10})$ heterocyclyl,  
 (ii) heteroaryl,  
 (iii)  $(C_4-C_{10})$ cycloalkyl unsubstituted or substituted with  $(C_1-C_6)$ alkyl, or  
 (iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro,  $(C_1-C_{10})$ alkyl,  $(C_1-C_{10})$ alkoxy, halo- $(C_1-C_3)$ alkoxy, halo- $(C_1-C_3)$ alkyl,  $(C_1-C_3)$ alkoxy-phenyl, phenyl, phenyl- $(C_1-C_3)$ alkyl,  $(C_1-C_6)$ alkoxypyhenyl, phenyl- $(C_1-C_3)$ alkynyl, and  $(C_1-C_6)$ alkyl-phenyl;  
 55 f)  $(C_4-C_{10})$ cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:  
 (i)  $(C_1-C_6)$ alkyl,

(ii) ( $C_1$ - $C_6$ )alkoxy,  
 (iii) ( $C_1$ - $C_6$ )alkenyl,  
 (iv) ( $C_1$ - $C_6$ )alkynyl,  
 (v) ( $C_4$ - $C_{10}$ )cycloalkyl,  
 5 (vi) phenyl,  
 (vii) phenylthio,  
 (viii) phenyl substituted by nitro, halo, ( $C_1$ - $C_6$ )alkanoyloxy, or carbocycloalkoxy, and  
 (ix) a group represented by the formula -Z-R<sup>13</sup> wherein Z and R<sup>13</sup> are as defined above; and  
 g) a group of the formula:

10



15

wherein

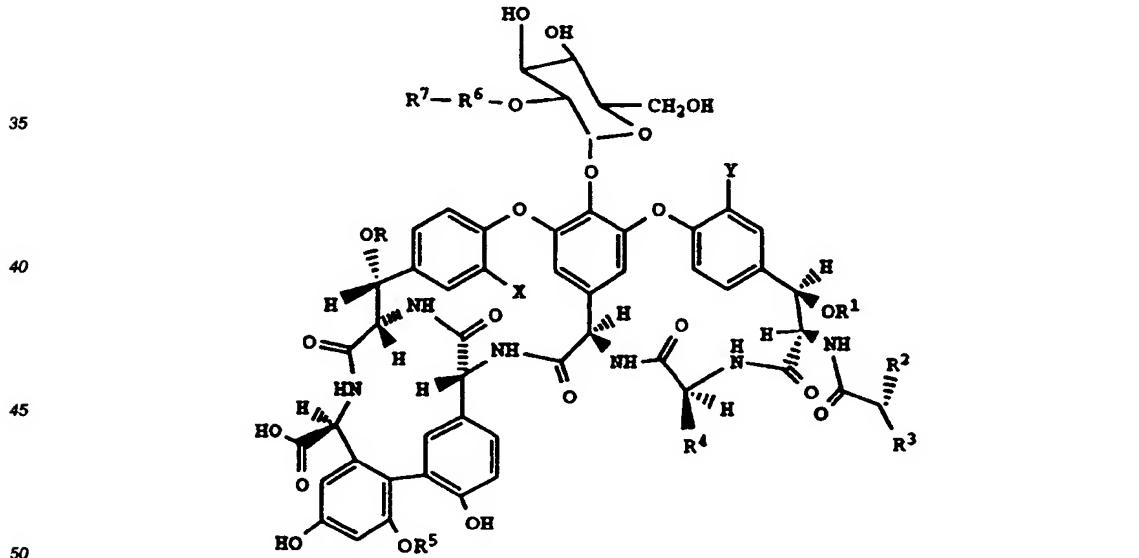
 $A^3$  and  $A^4$  are each independently selected from

(i) a bond,  
 (ii) -O-,  
 20 (iii) -S(O)<sub>t</sub>, wherein t is 0 to 2,  
 (iv) -C(R<sup>17</sup>)<sub>2</sub>, wherein each R<sup>17</sup> substituent is independently selected from hydrogen, ( $C_1$ - $C_6$ )alkyl, hydroxy, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, or both R<sup>17</sup> substituents taken together are O,  
 (v) -N(R<sup>18</sup>)<sub>2</sub>, wherein each R<sup>18</sup> substituent is independently selected from hydrogen; ( $C_1$ - $C_6$ )alkyl; ( $C_1$ - $C_6$ )alkenyl; ( $C_1$ - $C_6$ )alkynyl; ( $C_4$ - $C_{10}$ )cycloalkyl; phenyl; phenyl substituted by nitro, halo, ( $C_1$ - $C_6$ )alkanoyloxy; or both R<sup>18</sup> substituents taken together are ( $C_4$ - $C_{10}$ )cycloalkyl;  
 25  $R^{16}$  is  $R^{12}$  or  $R^{13}$  as defined above; and  
 u is 0-4.

20

## 2. A compound of the formula:

30



35

or salt thereof, wherein:

X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-epi-vancosaminy, actinosaminy, or ristosaminy;

40

R^1 is hydrogen, or mannose;

R^2 is -NH<sub>2</sub>, -NHCH<sub>3</sub>, or -N(CH<sub>3</sub>)<sub>2</sub>;55 R^3 is -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, phenyl, [*p*-OH,*m*-Cl]phenyl, *p*-rhamnose-phenyl, or [*p*-rhamnose-galactose]phenyl;

5 R<sup>4</sup> is -CH<sub>2</sub>(CO)NH<sub>2</sub>, benzyl, [*p*-OH]phenyl, or [*p*-OH, *m*-Cl]phenyl;

R<sup>5</sup> is hydrog n, or mannose;

R<sup>6</sup> is 4- *p*-vancosaminyl, L-acosaminyl, L-ristosaminyl, or L-actinosaminyl;

R<sup>7</sup> is -(CH<sub>2</sub>)<sub>n</sub>R<sup>8</sup>, or -C(CH<sub>3</sub>)CH-R<sup>8</sup>, and is attached to the amino group of R<sup>6</sup>;

n is 1-10;

R<sup>8</sup> is selected from the group consisting of:

a) multicyclic aryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

10 (i) hydroxy,

(ii) halo,

(iii) nitro,

(iv) (C<sub>1</sub>-C<sub>6</sub>)alkyl,

(v) (C<sub>1</sub>-C<sub>6</sub>)alkenyl,

(vi) (C<sub>1</sub>-C<sub>6</sub>)alkynyl,

15 (vii) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(viii) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

(ix) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(x) carbo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(xi) carbobenzoyloxy,

20 (xii) carbobenzoyloxy substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro,

(xiii) a group of the formula -S(O)<sub>n</sub>-R<sup>9</sup>, wherein n' is 0-2 and R<sup>9</sup> is (C<sub>1</sub>-C<sub>6</sub>)alkyl, phenyl, or phenyl substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, halo, or nitro, and

25 (xiv) a group of the formula -C(O)N(R<sup>10</sup>)<sub>2</sub> wherein each R<sup>10</sup> substituent is independently hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, phenyl, or phenyl substituted with (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, halo, or nitro;

b) heteroaryl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

30 (i) halo,

(ii) (C<sub>1</sub>-C<sub>6</sub>)alkyl,

(iii) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(iv) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,

(v) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

(vi) phenyl,

(vii) thiophenyl,

35 (viii) phenyl substituted with halo, (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkenyl, (C<sub>1</sub>-C<sub>6</sub>)alkynyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, or nitro,

(ix) carbo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,

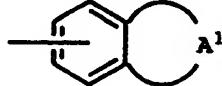
(x) carbobenzoyloxy,

(xi) carbobenzoyloxy substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>) alkoxy, halo, or nitro,

40 (xii) a group of the formula -S(O)<sub>n</sub>-R<sup>9</sup>, as defined above, and

(xiii) a group of the formula -C(O)N(R<sup>10</sup>)<sub>2</sub> as defined above;

c) a group of the formula:



50 wherein A<sup>1</sup> is -OC(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-O-, -O-C(A<sup>2</sup>)<sub>2</sub>-O-, -C(A<sup>2</sup>)<sub>2</sub>-O-, or -C(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-C(A<sup>2</sup>)<sub>2</sub>-O-, and each A<sup>2</sup> substituent is independently selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, (C<sub>1</sub>-C<sub>6</sub>)-alkoxy, and (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl;

d) a group of the formula:

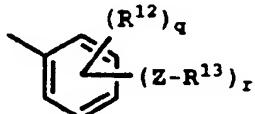


wherein p is from 1 to 5; and

R<sup>11</sup> is independently selected from the group consisting of:

- (i) nitro,
- (ii) hydroxy,
- (iii) (C<sub>1</sub>-C<sub>12</sub>)alkyl,
- (iv) (C<sub>1</sub>-C<sub>12</sub>)alkoxy,
- (v) (C<sub>2</sub>-C<sub>6</sub>)alkenyoxy,
- (vi) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,
- (vii) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,
- (viii) (C<sub>2</sub>-C<sub>6</sub>)alkylthio,
- (ix) (C<sub>1</sub>-C<sub>6</sub>)alkynyl,
- (x) (C<sub>2</sub>-C<sub>10</sub>)alkanoyloxy,
- (xi) carboxy-(C<sub>2</sub>-C<sub>4</sub>)alkenyl,
- (xii) (C<sub>1</sub>-C<sub>3</sub>)alkylsulfonyloxy,
- (xiii) carboxy-(C<sub>1</sub>-C<sub>3</sub>)alkyl,
- (xiv) (C<sub>1</sub>-C<sub>3</sub>)alkoxy substituted with (C<sub>1</sub>-C<sub>3</sub>)alkoxy, hydroxy, halo(C<sub>1</sub>-C<sub>3</sub>)alkoxy, or (C<sub>1</sub>-C<sub>4</sub>)alkylthio,
- (xv) N-[di(C<sub>1</sub>-C<sub>3</sub>)-alkyl]amino-(C<sub>1</sub>-C<sub>3</sub>)alkoxy,
- (xvi) cyano-(C<sub>1</sub>-C<sub>6</sub>)alkoxy,
- (xvii) (C<sub>1</sub>-C<sub>12</sub>)alkyl, (C<sub>1</sub>-C<sub>12</sub>)alkoxy, or halo when p is greater or equal to 2,
- (xviii) diphenyl-(C<sub>1</sub>-C<sub>6</sub>)alkyl, and
- (xix) hydrogen, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or (C<sub>1</sub>-C<sub>6</sub>)alkoxy when n greater or equal to 4;

e) a group of the formula:



wherein q is 0 to 4;

R<sup>12</sup> is independently selected from the group consisting of:

- (i) halo,
- (ii) nitro,
- (iii) (C<sub>1</sub>-C<sub>6</sub>)alkyl,
- (iv) (C<sub>1</sub>-C<sub>6</sub>)alkoxy,
- (v) halo-(C<sub>1</sub>-C<sub>6</sub>)alkyl,
- (vi) halo-(C<sub>1</sub>-C<sub>6</sub>)alkoxy, and
- (vii) hydroxy, and
- (viii) (C<sub>1</sub>-C<sub>6</sub>)thioalkyl;

r is 1 to 5; provided that the sum of q and r is no greater than 5;

Z is selected from the group consisting of:

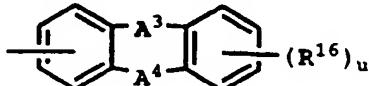
- (i) a single bond,
- (ii) divalent (C<sub>1</sub>-C<sub>6</sub>)alkyl unsubstituted or substituted with hydroxy, (C<sub>1</sub>-C<sub>6</sub>)alkyl, or (C<sub>1</sub>-C<sub>6</sub>)alkoxy,
- (iii) divalent (C<sub>2</sub>-C<sub>6</sub>)alkenyl,
- (iv) divalent (C<sub>2</sub>-C<sub>6</sub>)alkynyl, or
- (v) a group of the formula -(C(R<sup>14</sup>)<sub>2</sub>)<sub>s</sub>-R<sup>15</sup>- or -R<sup>15</sup>-(C(R<sup>14</sup>)<sub>2</sub>)<sub>s</sub>-, wherein s is 0-6; each R<sup>14</sup> substituent is independently selected from hydrogen, (C<sub>1</sub>-C<sub>6</sub>)-alkyl, or (C<sub>4</sub>-C<sub>10</sub>) cycloalkyl; and R<sup>15</sup> is selected from -O-, -S-, -SO-, -SO<sub>2</sub>-, -SO<sub>2</sub>O-, -C(O)-, -OC(O)-, -C(O)O-, -NH-, -N(C<sub>1</sub>-C<sub>6</sub> alkyl)-, and -C(O)NH-;

R<sup>13</sup> is independently selected from the group consisting of:

- (i) (C<sub>4</sub>-C<sub>10</sub>)heterocyclyl,
- (ii) heteroaryl,
- (iii) (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl unsubstituted or substituted with (C<sub>1</sub>-C<sub>6</sub>)alkyl, or
- (iv) phenyl unsubstituted or substituted with 1 to 5 substituents independently selected from: halo, hydroxy, nitro, (C<sub>1</sub>-C<sub>10</sub>) alkyl, (C<sub>1</sub>-C<sub>10</sub>)alkoxy, halo-(C<sub>1</sub>-C<sub>3</sub>)alkoxy, halo-(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>3</sub>)alkoxy-phenyl, phenyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)alkyl, (C<sub>1</sub>-C<sub>6</sub>)alkoxypyhenyl, phenyl-(C<sub>1</sub>-C<sub>3</sub>)alkynyl, and (C<sub>1</sub>-C<sub>6</sub>)alkyl-phenyl;

f) (C<sub>4</sub>-C<sub>10</sub>)cycloalkyl unsubstituted or substituted with one or more substituents independently selected from the group consisting of:

(i) ( $C_1$ - $C_6$ )alkyl,  
 (ii) ( $C_1$ - $C_6$ )alkoxy,  
 (iii) ( $C_1$ - $C_6$ )alkenyl,  
 (iv) ( $C_1$ - $C_6$ )alkynyl,  
 5 (v) ( $C_4$ - $C_{10}$ )cycloalkyl,  
 (vi) phenyl,  
 (vii) phenylthio,  
 (viii) phenyl substituted by nitro, halo, ( $C_1$ - $C_6$ )alkanoyloxy, or carbocycloalkoxy, and  
 10 (ix) a group represented by the formula -Z-R<sup>13</sup> wherein Z and R<sup>13</sup> are as defined above; and  
 g) a group of the formula:



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wherein

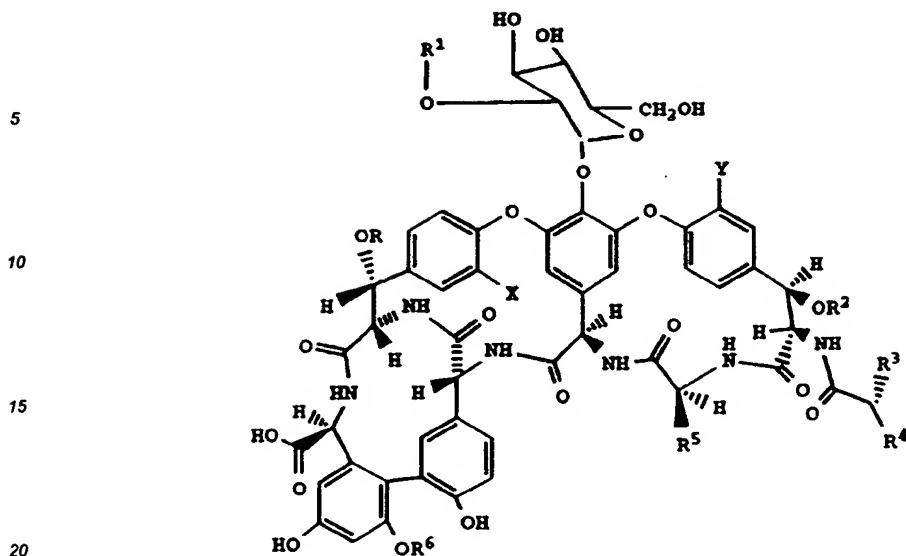
A<sup>3</sup> and A<sup>4</sup> are each independently selected from

(i) a bond,  
 20 (ii) -O-,  
 S(iii) -(O)<sub>t</sub>, wherein t is 0 to 2,  
 (iv) -C(R<sup>17</sup>)<sub>2</sub>, wherein each R<sup>17</sup> substituent is independently selected from hydrogen, ( $C_1$ - $C_6$ )alkyl, hydroxy, ( $C_1$ - $C_6$ )alkyl, ( $C_1$ - $C_6$ )alkoxy, or both R<sup>17</sup> substituents taken together are O,  
 25 (v) -N(R<sup>18</sup>)<sub>2</sub>, wherein each R<sup>18</sup> substituent is independently selected from hydrogen; ( $C_1$ - $C_6$ )alkyl; ( $C_1$ - $C_6$ )alkenyl; ( $C_1$ - $C_6$ )alkynyl; ( $C_4$ - $C_{10}$ )cycloalkyl; phenyl; phenyl substituted by nitro, halo, ( $C_1$ - $C_6$ )alkanoyloxy; or both R<sup>18</sup> substituents taken together are ( $C_4$ - $C_{10}$ )cycloalkyl;  
 R<sup>16</sup> is R<sup>12</sup> or R<sup>13</sup> as defined above; and  
 u is 0-4.

30 3. A compound of Claim 1 wherein R is 4-*epi*-vancosaminy, R<sup>1</sup> is hydrogen, R<sup>2</sup> is NHCH<sub>3</sub>, R<sup>3</sup> is CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, R<sup>4</sup> is CH<sub>2</sub>(CO)NH<sub>2</sub>, R<sup>5</sup> is hydrogen, R<sup>6</sup> is 4-*epi*-vancosaminy, and X and Y are Cl.  
 4. A compound of Claim 2 wherein R is 4-*epi*-vancosaminy, R<sup>1</sup> is hydrogen, R<sup>2</sup> is NHCH<sub>3</sub>, R<sup>3</sup> is CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, R<sup>4</sup> is CH<sub>2</sub>(CO)NH<sub>2</sub>, R<sup>5</sup> is hydrogen, R<sup>6</sup> is 4-*epi*-vancosaminy, and X and Y are Cl.  
 35 5. The compound 4-[4-chlorophenyl]benzyl-A82846B.  
 6. A pharmaceutical composition comprising a compound of Claim 1 to 5 or a pharmaceutically acceptable salt thereof, associated with one or more pharmaceutically acceptable carriers therefor.  
 40 7. A pharmaceutical composition as claimed in Claim 6 for use in treating susceptible bacterial infections.  
 8. A process for the preparation of a compound of any one of Claims 1 to 5 which comprises  
 45 a) reacting in methanol at about 25°C to about 100°C under an inert atmosphere:  
 i) a glycopeptide antibiotic of the formula:

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wherein X and Y are each independently hydrogen or chloro;

R is hydrogen, 4-*epi*-vancosaminy, actinosaminy, or ristosaminy;

R<sup>1</sup> is 4-*epi*-vancosaminy, acosaminy, ristosaminy, 4-keto-vancosaminy, or vancosaminy;

R<sup>2</sup> is hydrogen, or mannose;

R<sup>3</sup> is -NH<sub>2</sub>, -NHCH<sub>3</sub>, or N(CH<sub>3</sub>)<sub>2</sub>;

R<sup>4</sup> is -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, [p-OH, m-Cl]phenyl, p-rhamnose-phenyl, [p-rhamnose-galactose]phenyl, [p-galactose-galactose]phenyl, or [p-CH<sub>3</sub>O-rhamnose]phenyl;

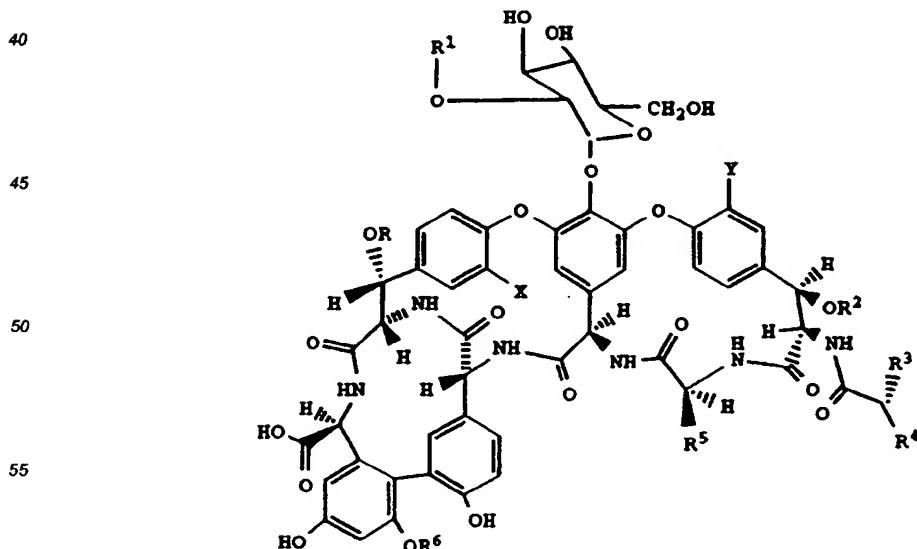
R<sup>5</sup> is -CH<sub>2</sub>(CO)NH<sub>2</sub>, benzyl, [p-OH]phenyl, or [p-OH, m-Cl]phenyl;

R<sup>6</sup> is hydrogen, or mannose, with

- ii) an aldehyde corresponding to the group R<sup>7</sup> as defined in Claim 1 at about 25°C to about 100°C;
- b) continuing the reaction until formation of a Schiff's base; and
- c) reducing the Schiff's base by addition of a metal borohydride to the mixture at 25°C to about 100°C.

35 9. A process for the preparation of a compound of any one of Claim 1 to 5 which comprises reacting in a polar solvent at about 25°C to about 100°C under an inert atmosphere:

- i) a glycopeptide antibiotic of the formula:



wherein X and Y are each independently hydrogen or chloro;  
R is hydrogen, 4-*epi*-vancosaminyI, actinosaminyI, or ristosaminyI;  
R<sup>1</sup> is 4-*epi*-vancosaminyI, acosaminyI, ristosaminyI, 4-keto-vancosaminyI, or vancosaminyI;  
R<sup>2</sup> is hydrogen, or mannose;  
R<sup>3</sup> is -NH<sub>2</sub>, -NHCH<sub>3</sub>, or -N(CH<sub>3</sub>)<sub>2</sub>;  
R<sup>4</sup> is -CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, [*p*-OH, *m*-Cl]phenyl, *p*-rhamnose-phenyl, [*p*-rhamnose-galactose]phenyl, [*p*-galactose-galactose]phenyl, or [*p*-CH<sub>3</sub>O-*r*-hamnose]phenyl;  
R<sup>5</sup> is -CH<sub>2</sub>(CO)NH<sub>2</sub>, benzyl, [*p*-OH]phenyl, or [*p*-OH, *m*-Cl]phenyl;  
R<sup>6</sup> is hydrogen, or mannose, with  
ii) an aldehyde corresponding to the group R<sup>7</sup> as defined in Claim 1, in the presence of  
iii) a reducing agent selected from a metal borohydride, and a homogeneous or heterogeneous catalytic  
hydrogenation agent or agents;  
for a time sufficient to produce a compound of Claim 1.

15 10. The process of Claim 9 wherein the reducing agent is sodium cyanoborohydride, and the reaction is carried out for about 20 to 28 hours at a temperature of about 60°C to about 70°C.  
11. The process of Claim 9 wherein the aldehyde is 4'biphenylcarboxaldehyde.

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## EUROPEAN SEARCH REPORT

Application Number  
EP 95 30 0429

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)
A	JOURNAL OF ANTIBIOTICS., vol.42, no.1, January 1989, TOKYO JP page 63-72 R NAGARAJAN ET AL. 'Synthesis and antibacterial evaluation of N-alkyl vancomycins' * the whole document * ---	1-10	C07K9/00 A61K38/14
X	EP-A-0 201 251 (ELI LILLY) 12 November 1986 * the whole document * ---	1-10	
D,A	EP-A-0 435 503 (ELI LILLY) 3 July 1991 * the whole document * -----	1-10	
TECHNICAL FIELDS SEARCHED (Int.Cl.)			
C07K A61K			
The present search report has been drawn up for all claims			
Place of search  THE HAGUE	Date of completion of the search  9 May 1995	Examiner  Masturzo, P	
CATEGORY OF CITED DOCUMENTS		I : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document	
X : particularly relevant if taken alone V : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			